British Journal of Diseases of the Chest

EDITORS
J. R. BELCHER and J. SMART

Volume LV No. 1 January, 1961

PUBLISHED QUARTERLY BY
BAILLIÈRE, TINDALL & COX
7 and 8 Henrietta Street, London, WC2

British Journal of Diseases of the Chest

Incorporating the British Journal of Tuberculosis and Diseases of the Chest

NOTICE TO CONTRIBUTORS

The British Journal of Diseases of the Chest is intended for the publication of papers on all aspects of diseases of the chest, tuberculosis and cognate subjects. Papers dealing with original work and investigations of clinical cases not previously published are especially invited.

All manuscript and editorial communications should be sent to the publishers of the *Journal* at 7 and 8 Henrietta Street, London, WC2. Papers accepted for publication become the copyright of the *Journal* and permission for re-publication elsewhere must be obtained from the Editors. Papers, which should be as concise as possible, are accepted on the understanding that they are subject to editorial revision and that they are contributed to this journal only. They should, in general, include under separate headings an introduction to the subject, a description of cases or methods used, a critical discussion, conclusions and a short summary. This last is essential.

Manuscripts, which should be pruned vigorously and represent the final form of the material, should be typewritten in double-line spacing with wide margins. Hand-written corrections must be legible and should be kept to a minimum.

References should be cited in the text thus: Smith (1959); and the list of references given in alphabetical order at the end of the paper, thus: SMITH, X. Y. (1959): *Brit. J. Dis. Chest*, **53**, 73. The titles of journals should be abbreviated according to the World List of Scientific Periodicals.

Photographs and photomicrographs should be printed on glossy paper and should, if possible, be larger than the size desired for reproduction. X-ray films should not be submitted, but prints of them (preferably negative prints). The area to be reproduced (if less than the whole) of each photograph should be indicated on the back. Not more than six photographs can be accepted for any one article unless by special and exceptional arrangement. Drawings and diagrams should be done in black ink on Bristol board or stout white paper. Legends to illustrations should not be attached to photographs or drawings but should be typewritten on a separate sheet of paper.

One galley proof will be sent to the author, corrections to which should be limited to verbal alterations.

All other correspondence, including the dealing with reprints, subscriptions, advertisements, etc., should be sent to the publishers.

Authors are supplied with 20 free reprints printed on one side of the paper. Additional reprints can be supplied only in booklet form and it is regretted that they tend to be rather expensive especially when plates are included. A quotation may be obtained for such additional reprints and enquiries should be addressed to the Publishers not later than the date on which galley proofs of the article are returned to the Editors.

Annual subscription is 60s., post free (U.S.A. and Canada $9.50) payable in advance; single copies, 18s., or $3.00.

BAILLIÈRE, TINDALL AND COX LTD.
7 and 8 Henrietta Street, London, WC2
TEMple Bar 3386-7-8

British Journal of Diseases of the Chest

Incorporating the British Journal of Tuberculosis and Diseases of the Chest

Editors J. R. BELCHER *and* J. SMART

NOTICE TO CONTRIBUTORS

The British Journal of Diseases of the Chest is intended for the publication of papers on all aspects of diseases of the chest, tuberculosis and cognate subjects. Papers dealing with original work and investigations of clinical cases not previously published are especially invited.

All manuscript and editorial communications should be sent to the publishers of the *Journal* at 7 and 8 Henrietta Street, London, WC2. Papers accepted for publication become the copyright of the *Journal* and permission for re-publication elsewhere must be obtained from the Editors. Papers, which should be as concise as possible, are accepted on the understanding that they are subject to editorial revision and that they are contributed to this journal only. They should, in general, include under separate headings an introduction to the subject, a description of cases or methods used, a critical discussion, conclusions and a short summary. This last is essential.

Manuscripts, which should be pruned vigorously and represent the final form of the material, should be typewritten in double-line spacing with wide margins. Hand-written corrections must be legible and should be kept to a minimum.

References should be cited in the text thus: Smith (1959); and the list of references given in alphabetical order at the end of the paper, thus: SMITH, X. Y. (1959): *Brit. J. Dis. Chest*, 53, 79. The titles of journals should be abbreviated according to the World List of Scientific Periodicals.

Photographs and photomicrographs should be printed on glossy paper and should, if possible, be larger than the size desired for reproduction. X-ray films should not be submitted, but prints of them (preferably negative prints). The area to be reproduced (if less than the whole) of each photograph should be indicated on the back. Not more than six photographs can be accepted for any one article unless by special and exceptional arrangement. Drawings and diagrams should be done in *black* ink on Bristol board or stout white paper. Legends to illustrations should not be attached to photographs or drawings but should be typewritten on a separate sheet of paper.

One galley proof will be sent to the author, corrections to which should be limited to verbal alterations.

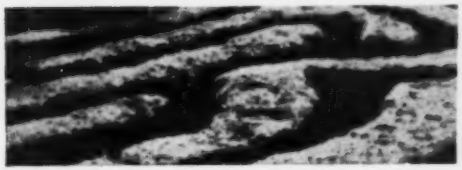
All other correspondence, including that dealing with reprints, subscriptions, advertisements, etc., should be sent to the publishers.

Authors are supplied with 20 free reprints printed on one side of the paper. Additional reprints can be supplied only in booklet form and it is requested that they tend to be rather expensive especially when plates are included. A quotation may be obtained for such additional reprints and enquiries should be addressed to the Publishers not later than the date on which galley proofs of the article are returned to the Editors.

Annual subscription is 60s., post free (U.S.A. and Canada $9.50) payable in advance; single copies, 18s., or $3.00.

BAILLIÈRE, TINDALL AND COX LTD.
7 and 8 Henrietta Street, London, WC2
TEMple Bar 3386-7-8

Through the maze of Streptomycins **follow the leader**



STREPTOMYCIN SULPHATE

Streptomycin Sulphate Glaxo
1 G vials in boxes of 10 5 G vials

Dry Stabilised Streptomycin Sulphate Glaxo
1 G vials in boxes of 10 5 G vials

STREPOLIN (Stabilised Injection of Streptomycin Sulphate Glaxo)
1 G vials (3 concentrations) in boxes of 10
5 G vials (3 concentrations)
1 G (2 ml) cartridges in wallets of 10

Streptomycin Sulphate for Intrathecal Injection Glaxo
50 mg ampoules in boxes of 5
100 mg ampoules in boxes of 5

STREPTOMYCIN CALCIUM CHLORIDE

Streptomycin Calcium Chloride Glaxo
1 G vials in boxes of 10 5 G vials

DIHYDROSTREPTOMYCIN SULPHATE

Dihydrostreptomycin Sulphate Glaxo
1 G vials in boxes of 10 5 G vials

STREPTODUOCIN
(Streptomycin and Dihydrostreptomycin)

DIMYCIN Dry Powder
1 G vials in boxes of 10 5 G vials

DIMYCIN Stabilised Injection
1 G (3 ml) vials in boxes of 10
5 G (15 ml) vials
1 G (2 ml) cartridges in wallets of 10

GLAXO

The Glaxo streptomycin service provides every form of streptomycin you can ask for. Two of them, often needed, have simplified names easy to remember and to write— DIMYCIN and STREPOLIN. The service is unique to Glaxo—first in Britain to manufacture streptomycin and still the country's leading producers.

STREPTOMYCIN GLAXO

GLAXO LABORATORIES LTD, GREENFORD, MIDDLESEX BYRon 3434

Subsidiary Companies or Agents in most countries. Dimycin and Strepolin are Glaxo trade marks

To face first page of text

Brit. J. Dis. Chest (1961) **55**, 1.

THE ERYTHROCYTE SEDIMENTATION RATE IN CARCINOMA OF THE BRONCHUS

By B. P. Harrold and P. R. Slade

St. Bartholomew's Hospital, London

The Erythrocyte Sedimentation Rate is an investigation commonly employed in cases suspected of being carcinoma of the bronchus. In order to try to assess the value of this investigation, a series of histologically proven cases of carcinoma of the bronchus has been studied.

The E.S.R. was estimated by the Westergren method and the estimation was made within the first few days after admission to hospital. Cases with a hæmoglobin of less than 10·4 grams per cent. have been excluded: Kourilsky (1952) has shown that the E.S.R. is not affected until the red cell count is below 3,500,000 per cu. mm.

The group studied was made up as follows:

	Cases
Oat cell carcinoma	63
Adenocarcinoma	32
Undifferentiated carcinoma	51
Squamous cell carcinoma	155
Total	301

Results

In these 301 cases of carcinoma of the bronchus the E.S.R. on first admission was:

E.S.R.	*No. of cases*	*% of total*
1 to 10 mm. in 1st hour	52	17·4
11 to 50 mm. in 1st hour	126	41·8
Over 50 mm. in 1st hour	123	40·8

When carcinomata of different cell types were studied separately (see Table I) it was found that adenocarcinomata had a considerably larger number (37·5 per cent.) with a normal E.S.R. The group of adenocarcinomata contained many more cases with peripheral tumours, lobectomy was performed in 34·4 per cent. of adenocarcinomata, but in only 15·9 per cent. of oat cell carcinomata, 15·7 per cent. of undifferentiated and in 15·5 per cent. of squamous cell carcinomata.

Effect of Coincident Infection

Forty-three cases (14·4 per cent. of the total) were considered to have significant lung infection at the time of the investigation. The incidence of infected cases was highest in the oat cell carcinomata, but did not differ very greatly in the different cell-type groups, occurring in oat cell 19·1 per cent., adenocarcinoma

(*Received for publication October* 1, 1960.)

TABLE I—E.S.R. RELATED TO TYPE OF CARCINOMA

Cell type	*E.S.R. 1 to 10 mm.*	*E.S.R. 11 to 50 mm.*	*E.S.R. over 50 mm.*
Oat cell carcinoma (63 cases)	9 (14·3%)	34 (54%)	20 (31·7%)
Adenocarcinoma (32 cases)	12 (37·5%)	14 (43·8%)	6 (18·7%)
Undifferentiated carcinoma (51 cases)	8 (15·7%)	22 (43·1%)	21 (41·2%)
Squamous cell carcinoma (155 cases)	23 (14·9%)	56 (36·1%)	76 (49%)

15·6 per cent., undifferentiated 13·7 per cent., squamous 12·2 per cent. In the 43 cases with infection the E.S.R. was:

	Cases
1 to 10 mm. in 1st hour	3
11 to 50 mm. in 1st hour	19
Over 50 mm. in 1st hour	21

It is likely that there is some element of infection in most cases of carcinoma of the bronchus, but in this series in only 43 was evidence of significant infection noted at the initial examination or found in the resected specimen. As might be expected the E.S.R. was raised in 93 per cent. of infected cases. In the 3 with a normal E.S.R. chest infection was the presenting feature, but had improved considerably at the time of admission.

Amongst the 301 cases of carcinoma there were 5 with hypertrophic pulmonary osteoarthropathy. In all of these the E.S.R. was above 20 mm. in the first hour.

THE STAGE OF THE DISEASE

An attempt has been made to correlate the E.S.R. with the extent of spread of the carcinoma. The findings in this respect are shown in Table II. The growth was confined to the lung or to the lung and intrapulmonary lymph nodes in 57·7 per cent. of cases with a normal E.S.R., but this stage of growth was only found in 34·9 per cent. of cases with a raised E.S.R. Only 2 with a normal

TABLE II.—E.S.R. RELATED TO SPREAD OF CARCINOMA

E.S.R. mm. in 1st hour	*Growth confined to lung or lung + broncho-pulmonary lymph nodes*	*Growth in lung and in mediastinal lymph nodes*	*Growth invading other thoracic organs or having distant metastases*
1-10 (52 cases)	30 cases (57·5%)	18 cases (34·6%)	4 cases (7·7%)
11-50 (126 cases)	47 cases (37·3%)	48 cases (38·1%)	31 cases (24·6%)
Over 50 (123 cases)	40 cases (32·5%)	32 cases (26·0%)	51 cases (41·5%)

TABLE III.—OVERALL SURVIVAL RATES FOR THE SERIES

Cell types	1 year		2 years		3 years		4 years		5 years	
	No. of possible survivors	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*
Oat cell	63	9	63	6	61	5	45	2	33	2
Adenocarcinoma ..	32	10	32	4	27	4	24	1	21	0
Undifferentiated ..	51	10	51	7	47	4	42	1	36	1
Squamous cell ..	155	62	155	33	139	21	110	17	98	5
All cell types ..	301	91	301	50	274	34	221	21	188	8

TABLE IV.—SURVIVAL RATES ACCORDING TO E.S.R. AND CELL TYPE

Cell type	Level of E.S.R.	1 year		2 years		3 years		4 years		5 years	
		No. of possible survivors	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*	*No. of possible survivors*	*No. of actual survivors*
Oat cell	1-10	9	4	9	0	7	0	6	0	3	0
	11-50	34	4	34	3	30	2	20	0	15	0
	50+	20	4	20	3	17	3	15	2	15	2
Adenocarcinoma ..	1-10	12	4	12	3	11	3	9	1	9	0
	11-50	14	4	14	0	11	0	8	0	6	0
	50+	6	2	6	1	5	1	4	0	2	0
Undifferentiated ..	1-10	8	2	8	2	8	1	7	0	6	0
	11-50	22	2	22	0	20	0	18	0	15	0
	50+	21	6	21	3	18	3	16	1	12	1
Squamous cell ..	1-10	23	10	23	3	20	3	12	2	11	1
	11-50	56	24	56	16	52	10	46	8	35	1
	50+	76	28	76	14	71	8	54	7	49	3
All cell types ..	1-10	52	20	52	8	49	7	38	3	34	1
	11-50	126	34	126	19	113	12	92	8	71	1
	50+	123	40	123	21	111	15	89	9	78	6

E.S.R. had distant metastases. A similar trend is shown by the treatment which was employed. Thus resection was performed in 78·8 per cent. (41 cases) when the E.S.R. was between 1 and 10 mm. in first hour, in 62·6 per cent. (79 cases) when E.S.R. was between 11 and 50 mm., and in 39·8 per cent. (49 cases) when the level was over 50 mm. in the first hour.

E.S.R. related to the Prognosis

The survival rates for this series of cases of carcinoma of the bronchus are shown in Table III. Only those treated by resection lived for two years or more. The prognosis in this disease is affected both by the cell type and by the extent of the growth. Table IV shows the survival figures related to cell type and level of E.S.R. and it is apparent that the E.S.R. is quite unreliable as a guide to prognosis. In all cell types, even with the E.S.R. within the normal range, less than half of the cases survive for one year. For oat cell, undifferentiated carcinomata, and for the group as a whole, the best long-term survival figures were in the group with E.S.R. over 50 mm. in the first hour. This may well be because infection has led to earlier diagnosis; one of those who survived five years with an oat cell carcinoma and one of the three-year survivors with undifferentiated carcinoma had had chest infection as a presenting feature.

Discussion

In carcinoma of the bronchus estimation of the E.S.R. might be expected to prove helpful from two aspects, diagnosis and extent or prognosis.

(1) *Diagnosis.*—The E.S.R. is usually raised in carcinoma of the bronchus. In this series the E.S.R. was abnormal in 82·6 per cent. of cases. However, a large number of the chest conditions which have to be distinguished from carcinoma of the bronchus have an element of infection and therefore a raised E.S.R. also. Thus Beresford (1952), in 2,733 cases at a cancer diagnosis clinic, found that the E.S.R. was over 10 mm. in first hour in 88·9 per cent. of proven cases of carcinoma of the bronchus, but also in 70·3 per cent. of the other pulmonary conditions.

During the period of this study, 27 cases were admitted in which there did not appear to be any element of infection. The small series of "simple tumours" was made up: tumours of neural tissue 6 cases, hamartomata 5 cases, parapericardial cysts 4 cases, lipomata 2 cases, sequestrated segments 2 cases, dermoids 4 cases, parabronchial cysts 4 cases. The level of E.S.R. found in these 27 patients was:

1 to 10 mm. in 1st hour	.. ..	17 cases (63%)
11 to 50 mm. in 1st hour	.. ..	9 „ (33·3%)
Over 50 mm. in 1st hour	.. ..	1 case (3·7%)

Thus, even in such a selected series, the E.S.R. is likely to be abnormal in over one-third of the cases. Since a raised E.S.R. is so commonly found in many different chest conditions, it is of very little help in the differential diagnosis of carcinoma of the bronchus. Indeed it is probably more important to stress

that a normal E.S.R. is found not infrequently with carcinoma of the bronchus and should never be held to invalidate the diagnosis of this disease.

(2) *Extent of the Disease.*—When the E.S.R. was normal the growth was confined to the lung or lung plus intrapulmonary lymph nodes more frequently and could more frequently be removed surgically than when the E.S.R. was raised. However, probably because of the influence of superadded infection in some cases, a normal E.S.R. was not necessarily found to be associated with the best long-term survival figures. Therefore, in any given case, the E.S.R. is a poor guide to prognosis.

Summary and Conclusion

1. The E.S.R. has been studied in a series of 301 cases of carcinoma of the bronchus.

2. The E.S.R. was found to be raised in 82·6 per cent. of these cases.

3. In adenocarcinomata the E.S.R. was normal in 37·5 per cent. cases.

4. With a normal E.S.R. the growth was confined to the lung or to the lung plus intrapulmonary nodes in 57·7 per cent. of cases.

5. The E.S.R. was not considered to be of much help in the differential diagnosis of cases of carcinoma of the bronchus.

6. The level of E.S.R. was not reliable in estimating the prognosis of carcinoma of the bronchus.

7. The E.S.R. is an investigation which appears to have very little value in this disease.

We should like to thank Mr. O. S. Tubbs and Mr. I. M. Hill for providing facilities for studying these patients and Dr. G. Canti and the technicians of his department for performing the E.S.R.

REFERENCES

BERESFORD, O. D. (1952): *Canad. med. Ass. J.*, **67**, 347.
KOURILSKY, R. (1952): *J. franç. Méd. Chir. thorac.*, **6**, 263.

Brit. J. Dis. Chest (1961) 55, 6.

THE RELATIONSHIP BETWEEN EFFORT INTOLERANCE, SPIROMETRY AND BLOOD GAS ANALYSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE

By J. Smart, S. Naimi and L. H. Capel
From the London Chest Hospital

In the management of patients with chronic obstructive airway disease, the assessment of effort intolerance, spirometry and blood gas analysis are often done. The results to be expected from these measurements and the significance of the relationships between them have often been investigated in the more seriously affected patients and in those with heart failure due to lung disease. There have been few investigations reported in which these measurements have been studied in groups of less severely disabled patients with chronic obstructive airway disease. Such studies might help the clinician to grade the severity of the disease, and they might help him in the differential diagnosis of the different forms of obstructive airway disease from each other and from other diseases of the lungs and heart. They might also help him to assess the clinical value of each test.

The relationship of effort intolerance of different grades of severity and the results of other lung function tests in patients with chronic obstructive airway disease has been studied by Miller, Fowler and Helmholtz (1953) and Sinclair (1955). Baldwin, Cournand and Richards (1949) in a classical study, and Platts and Greaves (1957), compared the results of blood gas analysis in patients with and without heart failure due to lung disease. Ogilvie (1959) has discussed the clinical and pathological significance of the relationship between spirometry and lung diffusing capacity.

This paper is a report of a pilot study of patients with chronic obstructive airway disease in which the relationships between effort intolerance and the results of the lung function tests commonly employed, spirometry and blood gas analysis, are compared. None of the patients were suffering from pulmonary heart disease at the time of the test. The forced expiratory volume was the spirometric recording used to measure the severity of airway obstruction. The effort intolerance grading used resembled that proposed by Fletcher (1952).

The Patients

These were in-patients and out-patients of the London Chest Hospital who were attending because of chronic cough, expectoration and breathlessness. It is probable that most British physicians would have agreed that the diagnosis of chronic bronchitis and emphysema might be applied to them. In

(*Received for publication September* 20, 1960.)

some the diagnosis of asthma with chronic bronchitis and emphysema might have been made.

The functional defect common to all of the patients was obstruction of the airways of the lungs. Evidence for this was the reduced forced expiratory volume and the reduced ratio of forced expiratory volume to forced vital capacity (below 75 per cent.) which was found in all patients but one. The latter had mild bronchitis. The use of this ratio in the recognition of obstructive airway disease as a cause of reduction in the F.E.V. and vital capacity has been discussed by Capel and Smart (1958). There were 38 male patients, mean age 52 years (range 19 to 68 years) and 6 female patients, mean age 51 years (range 26 to 70 years). The mean ratio of forced expiratory volume to forced vital capacity was 41·7 per cent. (range 26 to 81 per cent.) for the men, and 49·3 per cent. (range 30 to 68 per cent.) for the women. In none of the patients was the diagnosis of cor pulmonale made at the time of their examination.

The patients were selected for study as the opportunity proved convenient. A small number of patients with cardio-pulmonary disorders other than chronic bronchitis and emphysema were also studied for comparison.

Methods

Blood sampling: Blood was taken from the brachial artery with the patient lying down. A further specimen of blood was taken at the end of two minutes' exercise. The patient was required to do straight leg raising to an angle of 45° in time to a metronome at 15 cycles a minute. This was thought to provide a stint of exercise roughly proportional to the patient's size.

Blood gas analysis: Arterial blood oxygen saturation and carbon dioxide tension were estimated with a modified Haldane apparatus (Capel and Smart, 1960). Estimations were duplicated and these checked with 0·5 per cent. oxygen saturation and 1 volume per cent. carbon dioxide content. *p*H was determined to the nearest 0·01 unit using the Wynn electrode system. The partial pressure of carbon dioxide in arterial blood (pCO_2) was determined from Singer and Hastings' nomogram (1948). Arterial blood oxygen partial pressure was calculated from oxygen saturation per cent. assuming a blood *p*H of 7·4.

Effort intolerance grading: This was ascertained by questioning the patients in a standard way. According to their answers they were divided into six grades of effort intolerance. For descriptive purposes these grades were amalgamated into three, as follows:

Mild: able to maintain normal walking pace on level ground (grades 0, 1 and 2).

Moderate: unable to maintain normal walking pace on level ground (grades 3 and 4).

Severe: unable to walk about 100 yards slowly on level ground (grade 5).

The numerical value of the grade was used in calculating " Mean effort intolerance grade " (Table V).

Spirometry. The one second forced expiratory volume ($F.E.V._1$) and the forced vital capacity were measured as described before (Capel and Smart, 1958). The test was repeated after adrenaline spray inhalation. The $F.E.V._1$ was expressed as a percentage of the vital capacity expected for a healthy patient of the same age and height as the patient (Needham, Rogan and McDonald, 1954). This ratio was abbreviated F.E.V. per cent. p.V.C.

Results

1. *Effort Intolerance Grade related to Arterial Oxygen Saturation.*

Each patient's effort intolerance was graded as mild, moderate or severe, as described above. The mean of the arterial oxygen saturation measurements of the patients in each effort intolerance grade was calculated. In health arterial oxygen saturation is usually between 95 and 97 per cent., equivalent to an arterial oxygen partial pressure of 80 to 100 mm. Hg.

Table I

The relationship between the effort intolerance grades and the mean of the arterial blood oxygen saturation measurements, taken at rest, of the patients in each grade. The pO_2 was calculated from mean saturation.

Effort tolerance	*No. of patients*	*Art. O_2 sat.*	*pO_2*	*Range %*
Mild	9	94·2	74	93-96
Moderate ..	19	91·6	66	78-96
Severe	16	87·1	55·5	78-90

As effort intolerance increased, so mean arterial oxygen saturation at rest decreased progressively: 94·2, 91·6, 87·1 per cent. (Table I). These are equivalent to oxygen partial pressures of 74 mm. Hg, 66 mm. Hg and 55 mm. Hg respectively.

The scatter of the results was considerable. The lowest saturation found in the patients with mild effort intolerance was 93 per cent., while the highest saturation in the severely disabled group was 90 per cent. The range of satura-

Table II

The relationship between the effort intolerance grades and the mean value of the measurements of the fall in arterial oxygen saturation in the patients in each grade after light exercise. The pO_2 was calculated.

Effort tolerance	*No. of patients*	*Reduction in art. O_2 sat.%*	*pO_2*	*Range*
Mild	8	0·75	3·5	5/+2
Moderate ..	19	2·68	7·0	8/0
Severe	12	4·42	5·0	12/+4

tion of the patients with moderate effort intolerance completely overlapped the saturation of those with mild and those with severe effort intolerance (Table I).

As effort intolerance increased, so the reduction in the mean arterial oxygen saturation which followed exercise increased: 0·75, 2·68, 4·42 per cent. The scatter was considerable.

2. *Effort Intolerance related to Arterial Carbon Dioxide Partial Pressure (pCO_2)*

The effort intolerance of each patient was graded, and the patients were allotted to one of three groups as before. The mean of the arterial pCO_2 measurements of the patients in each group was calculated. The normal range of pCO_2 is 35-45 mm. Hg.

As effort intolerance increased, so there was a progressive increase in the mean resting arterial pCO_2: 36·5, 41·5, 44·2 mm. Hg (Table III).

TABLE III

The relationship between the effort intolerance grades and the mean of the arterial blood pCO_2 measurements, taken at rest, of the patients in each effort intolerance grade.

Effort tolerance	*No. of patients*	*Mean arterial pCO_2*	*Range*
Mild	8	36·5	28-45
Moderate	16	41·5	31-57
Severe	11	44·2	32-58

The scatter of the results was considerable. Patients with mild effort intolerance did not exceed the normal range of pCO_2, while the normal range was exceeded both by patients with moderate effort intolerance and patients with severe effort intolerance.

As effort intolerance increased, so there was a slight but progressive increase in the rise of arterial pCO_2 which followed exercise: 0·38, 1·44, 1·82 mm. Hg (Table IV).

TABLE IV

The relationship between the effort intolerance grades and the mean value of the rise in arterial blood pCO_2 in the patients in each grade after light exercise.

Effort tolerance	*No. of patients*	*Mean rise in pCO_2*	*Range*
Mild	8	0·38	−7/+5
Moderate ..	16	1·44	−2/+7
Severe	11	1·82	−2/+4

3. *The Forced Expiratory Volume related to Arterial Oxygen Saturation*

This relationship is shown in Table IV and Fig. 1. An $F.E.V._{\cdot 1}$ of 30 per cent. of the vital capacity predicted for the patient in health (F.E.V. per cent. p.V.C.) and an arterial saturation of 92 per cent. appeared to be critical values. In the majority of patients with an F.E.V. per cent. p.V.C. of more than

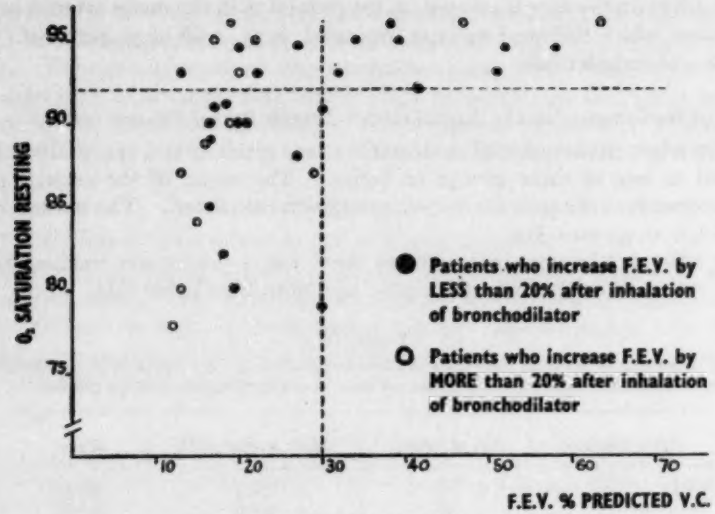


FIG. 1.—The F.E.V. related to arterial oxygen saturation.

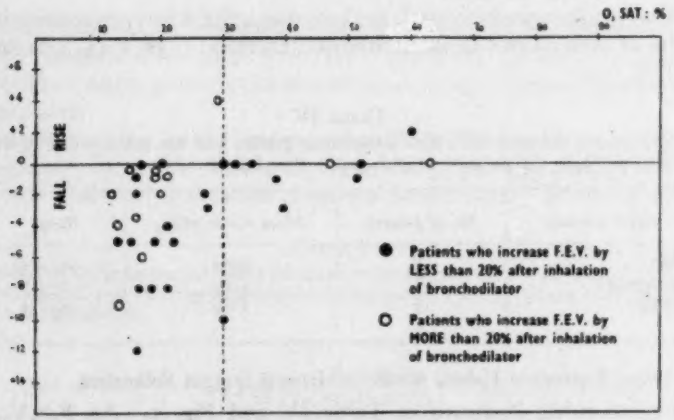


FIG. 2.—F.E.V. as a % of predicted Vital Capacity.

30 arterial oxygen saturation at rest was more than 92 per cent. In the majority with an F.E.V. per cent. p.V.C. of less than 30 arterial oxygen saturation at rest was less than 92 per cent. Thus the mean arterial oxygen saturation of the first group was 93 per cent. and of the second, 88·5 per cent. Conversely, the mean F.E.V. per cent. p.V.C. of patients with an arterial oxygen saturation of more than 92 per cent. was 33 and the mean value for those with a saturation of less than 92 per cent. was 19.

After exercise, the mean arterial oxygen saturation of patients with an F.E.V. per cent. p.V.C. of more than 30 fell by a mean 0·3 per cent. and for those with an F.E.V. per cent. p.V.C. of less than 30 it fell by a mean 1·96 per cent. (Fig. 2).

Among patients whose F.E.V. per cent. p.V.C. was less than 30 there was a smaller fall in arterial oxygen saturation after exercise in those able to increase their F.E.V. by more than 20 per cent. after adrenaline inhalation (mean fall in saturation 2·4 per cent.) than in those not able to do so (mean fall in saturation 4·2 per cent.).

4. *The Forced Expiratory Volume related to Arterial pCO_2*

This relationship is shown in Fig. 3. Until the F.E.V. per cent. p.V.C. fell below 30, arterial blood pCO_2 at rest remained within the normal range. Mean arterial blood pCO_2 at rest was 36 mm. Hg for those patients whose

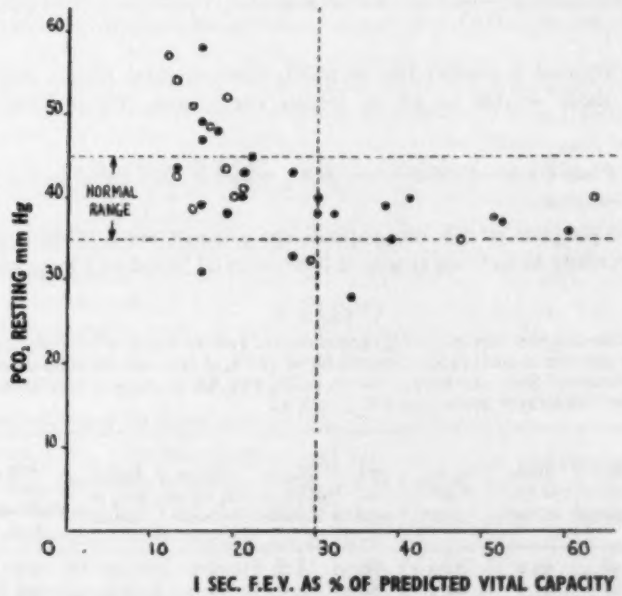


FIG. 3.—Relationship between 1 sec. Forced Expiratory Volume as a % of predicted Vital Capacity and resting pCO_2 in patients with obstructive airway disease.

F.E.V. per cent. p.V.C. was above 30, and 46·5 mm. Hg for those whose F.E.V. per cent. p.V.C. was below 30.

The effect of light exercise is shown in Fig. 4. The greatest rise in pCO_2 occurred in those patients whose F.E.V. per cent. p.V.C. was less than 30.

Among patients with an F.E.V. per cent p.V.C. of less than 30, those who were able to increase their F.E.V. by more than 20 per cent. after adrenaline

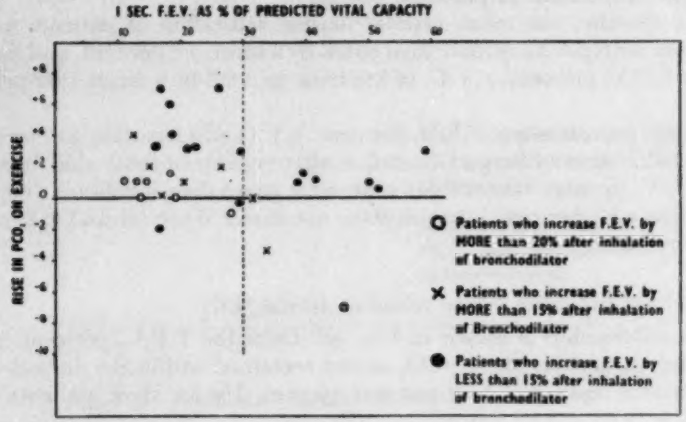


FIG. 4.—Relationship between 1 sec. Forced Expiratory Volume as a % of predicted Vital Capacity and rise in pCO_2 after exercise in patients with obstructive airway disease.

inhalation showed a smaller rise in pCO_2 after exercise (mean rise 0·2 mm. Hg) than those unable to do so (mean rise 3 mm. Hg). This is shown on Fig. 4.

5. *Arterial Blood Oxygen Saturation and pCO_2 related to Each Other, and to Spirometry and Effort Intolerance*

For the purpose of this comparison the patients were divided into three groups according to the magnitude of their arterial blood pCO_2 measurements:

TABLE V

The relationship between the pCO_2 ranges shown, and the mean of the following measurements of the patients in each range: arterial blood pCO_2 at rest, arterial oxygen saturation at rest, pO_2 calculated from saturation, rise in pCO_2 and fall in oxygen saturation after light exercise, effort intolerance grade and F.E.V. p.V.C.

pCO_2 at rest	*No. of patients*	*Mean pCO_2 at rest*	*O_2 sat. at rest*	*pO_2 at rest*	*Rise in pCO_2 on exercise*	*Fall in O_2 sat. on exercise*	*Fall in pO_2 on exercise*	*Mean effort intolerance grade*	*Mean F.E.V.% p.V.C.*
under 40	16	35·0	92·4	68	0·8	1·1	4·0	2·8	35·5
40-45	12	41·5	89·5	60·5	1·5	3·5	6·5	3·6	26·3
over 45	9	51·0	87·0	55	2·1	5·0	7·0	4·4	19·1

below 40 mm. Hg, 40-45 mm. Hg and above 45 mm. Hg (Table V). The mean value of the arterial blood pCO_2 of each of these groups was 35, 41·5 and 51 mm. Hg respectively. As the mean pCO_2 increased from group to group, so the mean arterial oxygen saturation diminished: 92·4, 89·5 and 87 per cent.; the mean effort intolerance grading increased 2·8, 3·6, and 4·4 and the mean F.E.V. per cent. p.V.C. diminished 35·5, 26·3 and 19·1. After exercise the mean arterial pCO_2 of each group rose by 0·8, 1·5 and 2·1 mm. Hg and the mean arterial oxygen saturation of each group fell by 1·1, 3·5 and 5·0 per cent. respectively.

Discussion

Though individual variation was considerable, there was a general pattern in the relationships between the results of the common respiratory function tests carried out in this group of patients with chronic obstructive airway disease. To show this general pattern, patients were allotted to one of three groups according to their arterial blood pCO_2 (Table V, just discussed), since this measurement closely reflects the efficiency of alveolar ventilation, the function most affected by obstructive airway disease.

As mean arterial pCO_2 increased from grade to grade, so mean arterial blood oxygen saturation and mean F.E.V. per cent. p.V.C. and mean effort tolerance decreased. After exercise, the mean rise in pCO_2 increased from grade to grade while the mean oxygen saturation decreased from grade to grade.

Baldwin *et al.* (1949) found a proportional relationship between maximum breathing capacity and a grading of the severity of emphysema by blood gas analysis. Maximum breathing capacity is closely related to the F.E.V. Capel and Smart (1959) described a proportional relationship between the F.E.V. and effort intolerance in men with chronic obstructive airway disease.

The pattern of results in patients with pulmonary fibrosis and in patients with heart disease is quite different. Their arterial blood pCO_2 is usually in the lower part of the normal range though slight arterial unsaturation and severe effort intolerance may be present. There may be a considerable fall in arterial oxygen saturation after exercise in patients with pulmonary fibrosis (because of the diffusion defect) without a rise in arterial pCO_2. In both these conditions the relationship of the F.E.V. to the vital capacity is quite different from that found in patients with chronic obstructive airway disease (Capel and Smart, 1958).

A Brief Interpretation of the Significance of Each of the Measurements

1. *Arterial pCO_2.* Of the three groups into which the patients were arbitrarily divided according to their arterial pCO_2, two spanned the normal range (35-45 mm. Hg) and the third exceeded it (above 45 mm. Hg). While arterial pCO_2 still remained within normal limits there was a sharp reduction in mean arterial oxygen saturation, mean F.E.V. per cent. p.V.C. and an increase in the severity of effort intolerance (Table 5). It is therefore probable that as a patient's chronic obstructive airway disease becomes more severe, so his arterial

pCO_2 increase through the normal range, to exceed it when the condition is far advanced.

In the earlier stages of the disease the patient is able to hyperventilate his lungs sufficiently to blow off carbon dioxide as fast as his body produces it. In the far advanced stage the severity of the airway obstruction prevents him from doing so.

In the individual patient measurement of arterial blood pCO_2 is evidently of little use in discriminating between the milder degrees of pulmonary insufficiency due to obstructive airway disease. On the other hand, the discovery that arterial blood pCO_2 is consistently above 45 mm. Hg is the best evidence for the presence of severe pulmonary insufficiency due to the condition: it means that the battle against carbon dioxide retention has been lost.

2. *Arterial blood oxygen saturation.* Though an arterial blood oxygen saturation of 92 per cent. is numerically near the normal figures of 95-97 per cent., it nevertheless indicates that the patient's arterial blood oxygen partial pressure may have fallen by about one-third from the normal figure of about 90 mm. Hg. Typically, a patient whose arterial blood oxygen saturation at rest is 92 per cent. would have some difficulty in maintaining normal walking pace on the level ground (Table V). The exercise of daily life might cause a further reduction in saturation. So might hypoventilation during sleep, if profound (Orie, 1959). A casual resting arterial sample may therefore give an underestimate of the severity of chronic anoxia in obstructive airway disease.

Arterial blood oxygen saturation reflects the severity of the damage to the alveoli. This is because it depends upon the ratio of ventilation to blood flow within them, and upon their capacity to diffuse oxygen into the blood stream. Arterial blood pCO_2 is independent of these, but it reflects the efficiency of alveolar ventilation, a function which has little effect on arterial oxygen saturation until alveolar ventilation is very greatly reduced. Comroe *et al.* (1955) and Campbell (1960) have reviewed this problem.

3. *The F.E.V.* The magnitude of the F.E.V. in chronic obstructive airway disease depends not only upon the condition of the airways, but also upon the condition of the alveoli. When the alveoli lose their elasticity they are no longer able to empty by their own contraction: chest wall pressure must therefore be exerted upon the lungs in order to empty them. Since this pressure falls equally upon the airways, which are thereby narrowed, and upon the alveoli, air is trapped within the lungs during expiration (Dayman, 1951; Campbell and others, 1957).

It is difficult to distinguish partially reversible airway obstruction (asthma and bronchitis) from irreversible damage to the respiratory bronchioles and alveoli (emphysema) as a cause of reduction of the F.E.V. In the patients studied here it seemed probable that partially reversible airway obstruction contributed to the reduction in the F.E.V. when the F.E.V. was increased by more than 20 per cent. after adrenaline inhalation. Mild effort intolerance associated with a low F.E.V. per cent. p.V.C. probably has the same significance (Capel and Smart, 1959).

If the reduction in arterial oxygen saturation and the rise in arterial pCO_2

after exercise was relatively small, this too suggested that partially reversible airway disease contributed to the reduction in the F.E.V., for patients in whom this occurred usually had a good adrenaline response (Figs. 2 and 4). Nevertheless, changes in the blood gases after exercise are difficult to interpret unless the experiment is done with great care. Standard exercise with arterial puncture is difficult to arrange, and the fitter " asthmatic " patients may exercise with greater vigour than the " emphysematous " ones. Two patients increased their arterial oxygen saturation after exercise, an event which has been noted by others.

4. *Effort intolerance.* Effort intolerance increased step by step with reduction in arterial oxygen saturation, with reduction in F.E.V. per cent. p.V.C. and with increase in arterial pCO_2. It was observed that a patient complaining of difficulty in maintaining normal walking pace on level ground might have an F.E.V. per cent. p.V.C. of less than half of the normal value, while his arterial blood oxygen saturation was still above 92 per cent. and his arterial pCO_2 still within the normal range (Table V). Spirometry was therefore the most sensitive guide to the presence of mild obstructive airway disease. From this it might be inferred that the difficulty which the patients experienced in ventilating their lungs was the most important cause of their mild or moderate effort intolerance.

Reduction of the F.E.V. per cent. p.V.C. to 30 appeared to be critical (Figs. 1 and 2). Above this figure arterial oxygen saturation remained above 92 per cent. and arterial pCO_2 within the normal range. Below this figure, arterial oxygen unsaturation and carbon dioxide retention of greater or lesser degree were common. If, in a patient with chronic obstructive airway disease, the F.E.V. per cent. p.V.C. is below 30, if the response of the F.E.V. to adrenaline inhalation is poor and if effort intolerance is moderate or severe, then a grave and permanent loss of respiratory reserve may have occurred.

5. *The scatter of the results.* The scatter of the results was considerable, as may be seen from the tables and figures. In an individual patient it was not possible to predict effort tolerance or any one of the repiratory function tests from a knowledge of any one of the others. Baldwin *et al.* (1949), Miller *et al.* (1953) and Sinclair (1955) made a similar observation. It is probable that as bronchial secretion and congestion, bronchiolar congestion and muscle spasm, air trapping from loss of alveolar elasticity and irreversible damage to respiratory bronchioles and alveoli (bronchitis, asthma and emphysema) each in different proportion contribute to total pulmonary disorder, so the patterns of the relationships between each of the clinical and experimental findings will change. The discovery and description of these patterns is one of the important future tasks of clinical respiratory function studies.

Summary

In a group of patients suffering from chronic obstructive airway disease, effort intolerance graded according to its severity, the forced expiratory volume, arterial blood oxygen saturation and arterial blood carbon dioxide partial pressure were recorded.

There were characteristic patterns in the relationships between these measurements which, it is suggested, are characteristic of chronic obstructive airway disease and of its severity. The scatter of the results was great; the patterns were therefore seen more clearly when the means of the measurements of groups of patients were compared, rather than in the individual case. Reasons for the scatter are discussed.

The value of using the measurements in combination in the diagnosis of the condition and in the assessment of its severity are discussed.

REFERENCES

BALDWIN, E. F., COURNAND, A., and RICHARDS, D. W. (1949): *Medicine*, **28**, 201.
CAMPBELL, E. J. M., MARTIN, H. B., and RILEY, R. L. (1957): *Bull. Johns Hopk. Hosp.*, **101**, 329.
CAMPBELL, E. J. M. (1960): In *Clinical Physiology*. Oxford: Blackwell, 1960.
CAPEL, L. H., and SMART, J. (1958): *Lancet*, **2**, 771.
(1959): *Lancet*, **1**, 960.
(1960): In preparation.
COMROE, J. H., FORSTER, R. E., DUBOIS, A. B., BRISCOE, W. A., and CARLSEN, E. A. (1955): *The Lung*. Chicago: Year Book Pub. Co.
DAYMAN, H. (1951) *J. clin. Invest.*, **30**, p. 1175.
FLETCHER, C. (1952): *Proc. roy. Soc. Med.*
MILLER, R. D., FOWLER, W. S., and HELMHOLTZ, H. F. (1953): *Bull. Johns Hopk. Hosp.*, **28**, 737.
NEEDHAM, C. D., ROGAN, M. C., and MCDONALD, I. (1954): *Thorax*, **9**, 313.
OGILVIE, C. (1959): *Thorax*, **14**, 113.
ORIE, N. G. M. (1959): *Adv. Cardiol.*, **2**, 319.
PLATTS, M. M., and GREAVES, M. S. (1957): *Thorax*, **12**, 236.
SINCLAIR, J. D. (1955) *Brit. J. Tuberc.*, **49**, p. 157.

Brit. J. Dis. Chest (1961) 55, 17.

REPAIR OF VENTRICULAR SEPTAL DEFECT FOLLOWING INDIRECT TRAUMA

By W. P. Cleland, The late Philip Ellman, John Goodwin and Arthur Hollman

From Leatherhead Hospital and the Departments of Medicine and Surgery, Hammersmith Hospital and Postgraduate Medical School of London, London

Defects in the ventricular septum are usually congenital in origin. Perforation of the septum as a result of extensive infarction due to occlusive coronary artery disease is well recognised, but rupture of the septum due to trauma is unusual, and has commonly been the result of stab wounds or extensive trauma to the chest. Ventricular septal defect following injury but without significant thoracic damage must be extremely rare. The following case report illustrates a possible case.

Case Report

The patient, a girl of 6 years, was perfectly well until, on February 19, 1959, she was knocked down by a motor vehicle in a minor accident. On admission to hospital there were no obvious signs of injury, no respiratory distress, and no pain in the chest. She vomited blood once. Hæmothorax, pneumothorax and fractures of the thoracic cage were absent. Because of tachycardia Dr. Bennett made a careful examination of the heart and found nothing abnormal. This had also been the case at a previous school examination.

The next morning she was noted to have a striking præcordial thrill, and the following day she was transferred to Hammersmith Hospital.

Clinical examination: She was a well-developed pale little girl without any obvious distress. There was a small left subconjunctival hæmorrhage, and some bruising in the lower posterior aspect of the left side of the chest.

Cardiovascular system: There was no cyanosis or clubbing of the fingers. The arterial pulse was regular: 150/minute, normal form. The femoral pulses were normal. Jugular venous pressure was +3 cm. above sternal angle, with augmented presystolic " a " wave.

The cardiac impulse consisted of a left ventricular thrust which was just palpable and there was a definite right ventricular lift. There was a full-length systolic thrill loudest at left lower sternal edge, and a loud and coarse Grade 4/4 pansystolic murmur in the same area. No diastolic murmurs were audible, but there was a third heart sound. Pulmonary valve closure was normal (Fig. 1). The blood pressure was 105/80. The spleen was impalpable. There were no signs of infective endocarditis.

Examination of the blood: The hæmoglobin was 12·3 g. per cent. and white blood cells 12,000/c. mm. The serum glutamic oxalacetic transaminase was 27 units (upper limit of normal 30 units). Cultures were negative.

Electrocardiography showed sinus tachycardia and suggested enlargement of both ventricles (Fig. 2).

(*Received for publication August* 16, 1960.)

Radiography showed a globular heart with enlargement of all chambers and main pulmonary arteries. The aortic arch was left-sided. Overfilling of lungs suggested increased pulmonary blood flow due to a left to right shunt. No evidence of hæmo- or pneumo-thorax or lung injury was present (Fig. 3).

Progress: A tentative diagnosis of traumatic ventricular septal defect was made. The child remained apprehensive but without symptoms, although neither bed rest nor digitalis influenced the tachycardia. There was no fever. On February 28 an apical mid-diastolic murmur attributable to increased mitral valve flow became audible (Fig. 1).

Cardiac catheterisation was performed on 18.3.59. The catheter was passed into the right atrium, right ventricle and pulmonary artery: the left atrium and left ventricle were not entered. Blood sampling indicated a rise in oxygen saturation in the right ventricle due to a left to right shunt at that level. Dye dilution curves were made with Coomassie blue dye injected into superior vena cava, right atrium and pulmonary artery, and revealed a left to right shunt of moderate size, but no right to left shunt. The arterial oxygen saturation was 96 per cent., the pulmonary blood flow 8·3 l./min. and the systemic blood flow 4·5 l./min. The pulmonary : systemic flow ratio was 1·9 : 1, and the pulmonary arteriolar resistance 1·2 units, total pulmonary vascular resistance being 3·6 units. The pulmonary arterial pressure was 46/17 mm. Hg, and the right ventricular pressure 46/4 mm. Hg. The pulmonary capillary venous (wedge) pressure was elevated: $a=23$, $x=14$, $v=39$, $y=16$ mm. Hg, with a mean of 20 mm. Hg. The right atrial pressure was 6 mm. Hg (mean).

Operation 25.3.60

Under total cardiopulmonary bypass (Dr. Melrose), the heart was explored by W. P. Cleland. The right ventricle was considerably enlarged and there was a systolic thrill over the outflow tract. There was a defect in the muscular portion of the ventricular septum near the apex measuring 3 × 1 cm. The surrounding septum appeared grey and fibrotic. The defect was closed with two layers of interrupted sutures. There was no damage to the tricuspid leaflets, but the valve ring was dilated. No other defects were found.

INTRACARDIAC PRESSURE MEASUREMENTS AT OPERATION (MM. HG)

	Before closure	*After closure*
Mid right ventricle	48/7	24/5
Systemic artery	74/52	85/50
Systolic RV/systemic pressure %	65	32

There was thus a satisfactory fall in right ventricular pressure after closure, indicating a normal pulmonary vasculature.

A biopsy from the edge of the defect was examined by Dr. M. B. Bishop, who reported as follows:

" The specimen is made up of a surface layer, underlying connective tissue and a minute fragment of cardiac muscle.

The section shows the following features:

The connective tissue is cellular, the cellular element being composed almost entirely of fibroblasts. At the surface these are arranged in a vertical direction, while more deeply they are horizontally disposed. Those near the surface are less mature than those more deeply placed. There is fibrin under-

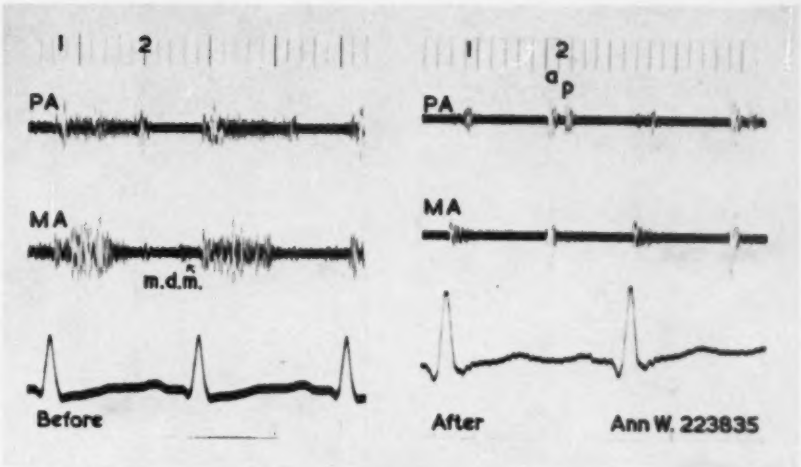


FIG. 1.—Phonocardiogram before and after closure of the ventricular septal defect. The louds ystolic murmur and the apical mid-diastolic murmur have disappeared, only a soft short systolic murmur remaining. The widely separated aortic and pulmonary components of the 2nd heart sound after operation reflect the right bundle branch block produced by the ventriculotomy.

PA = pulmonary area.
MA = mitral area (apex).
1 = 1st heart sound.
2 = 2nd heart sound.
m.d.m. = mid-diastolic murmur.
a = aortic valve closure.
p = pulmonary valve closure.

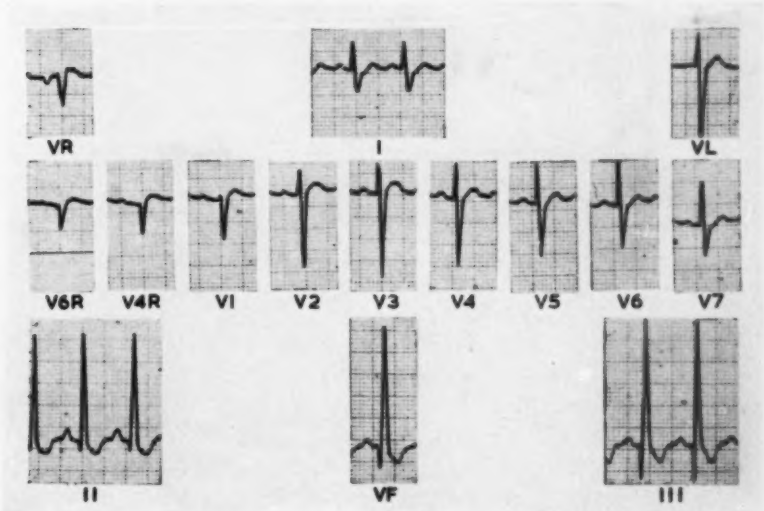


FIG. 2.—Electrocardiogram before operation. Sinus tachycardia. Deep S waves in praecordial leads, with tall R waves and prominent Q waves in Leads II, III and VF indicate enlargement of both ventricles.

To face p. 18

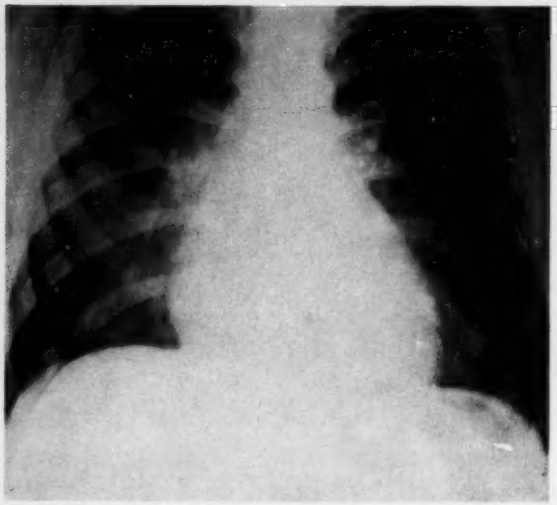
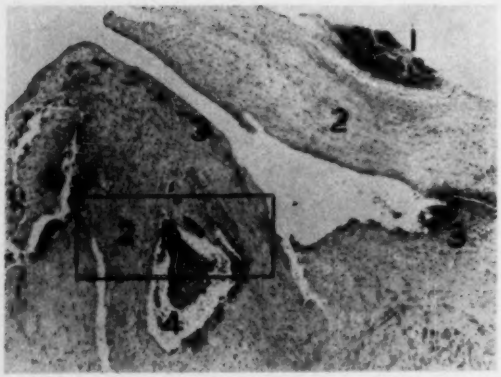


FIG. 3.—Six foot postero anterior radiograph of the chest before operation. The heart and pulmonary arteries are enlarged, and the pulmonary blood flow increased.



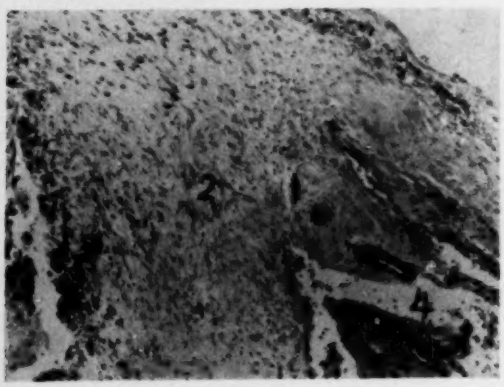


FIG. 4.—Photomicrographs of the biopsy taken from the edge of the ventricular septal defect. A. H & E×38. B. (rectangle) H & E×93.
1 = edge of ventricular muscle.
2 = fresh fibrous tissue.
3 = fibrosis.
4 = cellular focus with iron-containing macrophages.

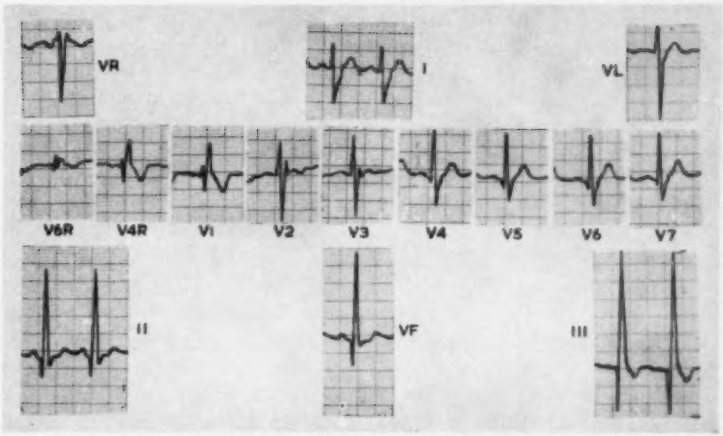


FIG. 5.—Electrocardiogram after operation showing right bundle branch block.

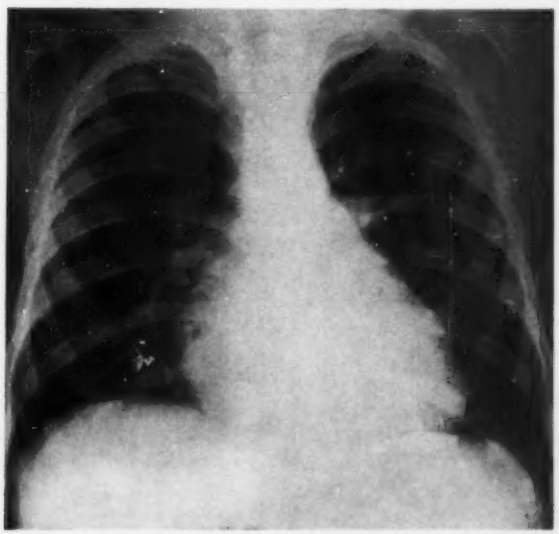


FIG. 6.—6 foot postero-anterior radiograph of the chest after operation. The heart is still enlarged but the pulmonary blood flow has been reduced.

going organisation in the deeper layers of this tissue. The collagenous component is immature, especially nearest to the surface. There are in addition histiocytes which contain iron pigment."

These features are not found in corresponding sections of known cases of congenital ventricular septal defect and indicate a recent healing process. They are therefore consistent with a traumatic lesion (Fig. 4).

The post-operative course was uneventful, and on discharge from hospital on 31.3.59 the jugular venous pressure was normal and the right ventricle quiet. The thrill had disappeared and only a faint (grade 1) short ejection murmur remained. The second heart sound was widely split as a result of the right bundle branch block which commonly follows closure of a ventricular septal defect (Fig. 5). The apical mid-diastolic murmur had disappeared.

Subsequent Progress

Twelve months after her operation the patient was well and active, able to swim without distress. On examination the heart was normal except for some enlargement of the right ventricle. The systolic murmur was quiet and the second heart sound still widely split (Fig. 1). The lung fields were normal on X-ray and there was no sign of a left to right shunt (Fig. 6). Cardiac catheterisation was not permitted by the parents and an intravenous dye dilution curve was unsuccessful.

It has been assumed on the basis of the physical signs and radiological appearances that the defect is completely closed.

Discussion

Although absolute proof is lacking, the inference that the defect in the ventricular septum was due to trauma is very strong. The patient had been carefully examined before and immediately after the accident, and no murmur or thrill was detected. Both were of such magnitude that they could scarcely have been missed. Furthermore, the character of the defect was totally different from that found in over 70 cases of congenital ventricular septal defect repaired at Hammersmith Hospital. Although a fibrous rim is not uncommon when the defect lies in the membranous septum, it is most unusual in a muscular defect. The appearance of the fibrous tissue suggested a recent inflammatory reaction, and this was confirmed by the histology, which indicated changes of healing quite consistent with recent trauma; no evidence of bacterial infection was found.

Presumably the septum was severely bruised in its muscular portion, the hæmatoma underwent softening, and ruptured in the twelve hours after the accident. The persistent tachycardia and considerably elevated left atrial pressure indicated left ventricular insufficiency, since there was no evidence of left atrial obstruction. The large acutely produced defect was tolerated remarkably well by the patient, presumably because her heart was previously normal. This is in sharp contrast to the severe and rapidly progressive heart failure which commonly follows a very small rupture of the septum after cardiac infarction. Such patients, however, are elderly and have severe generalised cardiac damage.

Non-penetrating injuries to the chest are well known to cause heart disease and hæmopericardium, pericarditis, myocardial contusion, rupture of papillary muscles, valve cusps and chordæ tendinæ have been documented. Traumatic rupture of the ventricular septum is uncommon but well recognised.

Hewett, in 1847, reported the case of a 5-year-old boy who died after a heavy cart had passed over his chest. Necropsy revealed a rupture in the ventricular septum at the junction of the lower third with the upper two-thirds of the septum, of 1-2 cm. in diameter.

In 1935 Bright and Beck reviewed all cases of non-penetrating cardiac injury; among these there were 11 cases of rupture of the ventricular septum.

In 1938 Warburg found 1 case of ventricular septal perforation in 51 cases of non-penetrating cardiac injury which came to necropsy.

Anderson (1940), and Bayrd and Gibson (1944), reported single cases suggestive of rupture of the ventricular septum, and East (1945) added another case, that of a man of 19 years who sustained a crushing injury to the chest. Mahaffey *et al.* (1957) reported successful closure of a ventricular septal defect resulting from a penetrating chest wound. Cary *et al.* (1958) reported 4 cases. Peirce *et al.* (1958) presented 24 proven cases from the literature and added one of their own in which closure was unsuccessfully attempted under hypothermia. Parmley *et al.* (1958) reported 30 instances of rupture of the ventricular septum (5 associated with aortic rupture) in 546 autopsy cases of non-penetrating injury to the heart. In 20, the ventricular wall also was ruptured, so that only 5 cases of isolated septal rupture occurred. Three of these survived for an unspecified period, and two were subsequently reported by other workers quoted in the present paper. The most common site of rupture of the septum in Parmley *et al.*'s cases was the muscular portion, the membranous portion being infrequently involved unless the perforation also occurred in the muscular portion.

Inkley and Barry (1958) reported 1 case of rupture of the ventricular septum proved by cardiac catheterisation, with survival. The chest injury was far more severe than in our case; the patient was struck forcibly from behind and his chest compressed against the platform of a milk truck, with resultant multiple rib fractures and surgical emphysema, and pneumothorax. No cardiac murmur was noted until at least three weeks following the accident, although it might have been undetectable earlier because of extracardiac sounds in the chest due to the other injuries.

Campbell *et al.* (1959) presented the first case to be successfully treated surgically by closure of the defect, and also reported on the further progress of the patient reported by Guilfoil and Doyle (1953).

There are thus around 29 proven cases of non-penetrating traumatic rupture of the ventricular septum, but the exact number is difficult to determine because of overlap in the reporting of cases. In the majority, further serious cardiac or other injuries have also been present, and, in every case except our own, there has been forcible direct injury to the thoracic cage.

Experimental animal work suggests that considerable blunt force is required to rupture the heart (Bright and Beck, 1935), the two factors apparently of

major importance being the direction of chest compression and the phase of the cardiac cycle in which the compression is applied. A full chamber in early systole is vulnerable if compressed over the outflow tract (Pollock *et al.*, 1952). Moritz and Atkins (1938) claimed that muscle fibres in groups of muscles may rupture at some distance from the site of trauma. Blunt force applied to the anterior chest may compress the heart, particularly if the blow occurs in diastole. Cardiac injury may thus occur in the absence of fractures of ribs, while serious cardiac damage is probably more likely to occur when the force is frontal and the heart is compressed between sternum and spine (Peirce *et al.*, 1958).

In our own case, injury to the chest was apparently trivial except for the cardiac damage. The absence of any evidence of other intra-thoracic injury tended to divert attention from the true diagnosis. Presumably muscle bundles in the septum were avulsed by contrecoup, perhaps during diastole, the resultant hæmatoma softening and rupturing some hours after the accident. It appears to be common for the murmur to be absent until some hours following the injury. External injury was also absent in one of Cary *et al.*'s (1958) cases, but severe respiratory distress, cyanosis and hypotension were evident.

The prognosis in this condition depends upon the presence and severity of associated lesions and the size of the defect produced. Peirce *et al.* (1958) believe that half such patients will die shortly after the injury unless the defect can be closed, but some undoubtedly do survive without closure, as shown by Anderson (1940), Bayrd and Gibson (1944), East (1945) and Campbell *et al.* (1959). The patient originally reported by Guilfoil and Doyle (1953) was still alive in 1957, although symptomatic, and his pulmonary arterial pressure and pulmonary blood flow had not significantly altered since 1951.

The immediate prognosis must depend upon the ability of the heart to withstand the extra load thrust upon it, and in this connection elevation of the left atrial pressure, as in our case, is presumably a sinister sign heralding overt left ventricular failure. It is of interest that the pulmonary capillary pressure was normal in the patient of Guilfoil and Doyle.

The site of rupture in the majority of reported cases has been in the muscular portion of the septum, suggesting that actively contracting muscle may be more vulnerable than the membranous portion of the septum.

The timing of operation to close the defect is of some importance. Clearly, if heart failure develops rapidly, then no time must be lost. But in our own case operation was deliberately postponed for several weeks in order to allow the development of firm fibrous tissue which would suture cleanly. Friable hæmatoma and œdematous muscle fibres would clearly make effective closure more difficult and hazardous. We believe, therefore, that meticulous medical treatment is indicated wherever possible for four to eight weeks after the rupture has occurred before operation is attempted.

Summary

A patient in whom rupture of the muscular portion of the ventricular septum apparently followed minor trauma to the chest is described. The condition was diagnosed clinically, confirmed by cardiac catheterisation, and success-

fully treated by closure under total cardio-pulmonary bypass. The literature has been briefly surveyed and the possible mechanisms of rupture commented upon. The case reported here appears to be the second of 29 reported cases successfully closed by surgical means.

We are grateful to the patient's general practitioners, Dr. Manclark and Dr. R. A. Bennett, for their clinical reports.

REFERENCES

ANDERSON, R. G. (1940): *Brit. med. J.*, **2**, 307.
BAYRD, E. D., and GIBSON, S. (1944): *J. Pediat.*, **24**, 138.
BRIGHT, E. F., and BECK, C. S. (1935): *Amer. Heart J.*, **10**, 293.
CAMPBELL, G. S., VERNIER, R. L., and LILLEHEI, C. W. (1959): *J. thorac. Surg.*, **37**, 496.
CARY, F. H., HURST, J. W., and ARENTZAN, W. R. (1958): *New Engl. J. Med.*, **258**, 355.
EAST, T. (1945): *Brit. Heart J.*, **7**, 116.
GUILFOIL, P. H., and DOYLE, J. T. (1953): *J. thorac. Surg.*, **25**, 510.
HEWETT, P. G. (1847): *Trans. path. Soc. Lond.*, **1**, 81.
INKLEY, S. R., and BARRY, F. M. (1958): *Circulation*, **18**, 916.
MAHAFFEY, D. E., SCHRAMEL, R., and CREECH, O., JR. (1957): *J. Louisiana State med. Soc.*, **109**, 321.
MORITZ, A. R., and ATKINS, J. P. (1938): *Arch. Path.*, **25**, 445.
PARMLEY, L. F., MANION, W. C., and MATTINGLEY, T. W. (1958): *Circulation*, **18**, 371.
PEIRCE, E. G. II, DOBBS, C. H., and ROWSON, F. L. (1958): *A.M.A. Arch. Surg.*, **77**, 87.
POLLOCK, B. E., MARKELZ, R. A., and SHUEY, H. E. (1952): *Amer. Heart J.*, **43**, 273.
WARBURG, L. (1938): *Subacute and Chronic Pericardial and Myocardial Lesions due to Non-penetrating Traumatic Injuries*. New York: Oxford University Press.

Brit. J. Dis. Chest (1961) 55, 23.

CHRONIC BRONCHITIS

CHANGES IN THE BACTERIAL FLORA OF THE SPUTUM ASSOCIATED WITH EXACERBATIONS AND LONG-TERM ANTIBACTERIAL TREATMENT

By Ann W. Cooper, G. M. Williamson and K. Zinnemann
Department of Bacteriology, School of Medicine, Leeds

and Gordon F. Edwards and Hilary Thornton
Leeds Chest Clinic

Edwards and others (1957) reported the results of an investigation into certain bacteriological aspects of the infective factor in chronic bronchitis, as well as those of a controlled therapeutic trial of oxytetracycline (Terramycin) alone or in combination with a triple sulphonamide (Sulphatriad) and autogenous vaccines of *Hæmophilus influenzæ*. A number of the patients observed in that study, who had been under observation since the winter of 1954-55, were more fully investigated during the winter months of 1956-57 and 1957-58 in an effort to determine the effect of oxytetracycline on the numerical incidence of *H. influenzæ* and the pneumococcus in the sputum. It was hoped that this investigation might elucidate the association of two of the more important potential pathogens in winter exacerbations of chronic bronchitis.

Materials and Methods

The patients admitted to the investigation were known from previous observation to harbour non-capsulated *H. influenzæ* reasonably consistently in their sputum, which was purulent most of the time. They were divided into two groups, one group receiving treatment during the first but not the second winter, the other receiving no treatment during the first but treatment during the second winter. In this way each patient served, at a different time, as his own control. Those treated were given 1 g. oxytetracycline together with an equal amount of triple sulphonamide daily during the six months from October to April. Indistinguishable dummy capsules and tablets were supplied to the patients in the untreated group.

Viable bacterial counts of *H. influenzæ* and of the pneumococcus as well as routine bacteriological examinations were carried out on sputa homogenised with liquid trypsin (Allen and Hanbury) as described by Rawlins (1953). Sputum specimens were examined as frequently as possible, and at least once a month.

Observations were started on 24 patients in October 1956. Owing to deaths or irregular attendances complete clinical records and regular specimens were available for the two winter periods for only 9 of the 24 patients. Of these 9 patients 4 were in the treatment group during 1956-57 and 5 in the control

(*Received for publication September* 14, 1960.)

group; during the winter season 1957-58, which coincided with the period of the first Asian influenza epidemic in this country, the position was reversed.

The 24 hr. volume and the naked eye appearance of the sputum was noted at each attendance at the follow-up clinic. Growth of the " five potential pathogens " (May 1954) in conventional culture was assessed after 24 and 48 hr. incubation and recorded as predominant, moderate or scanty. When *H. influenzæ* was not isolated, smears of the sputum stained by Gram and Leishman methods were examined for the presence or absence of Gram-negative coccobacilli, pus cells and eosinophil leucocytes. The number of *H. influenzæ* and pneumococci per ml. of sputum was determined by viable bacterial counts of serial ten-fold dilutions of homogenised sputa on chocolate agar plates containing 0·5 I.U. penicillin per ml. for *H. influenzæ* and 2 μg. streptomycin per ml. for the pneumococcus. Doubtful pneumococcus colonies were identified by the optochin test (Bowers and Jeffries, 1955) and doubtful *H. influenzæ* colonies were checked for their X and V requirements by the methods described by Zinnemann (1960). With this technique the least number of organisms per ml. of sputum that could be detected was 20,000. No other potential pathogens apart from *H. influenzæ* and the pneumococcus were found consistently and, therefore, only these two will be considered here.

Results

1. *The Initial Sputum Specimen*

Initial sputum specimens were avilable from 24 patients at the start in October 1956 but, owing to defaulting, from only 18 patients in October 1957. By culturing the first sputum specimens at the beginning of each winter season it was re-established that in these two groups of patients *H. influenzæ* was the predominant potential pathogen.

2. *Analysis and Assessment of H. influenzæ and Pneumococcus Counts*

a. Variation in density of H. influenzæ and the pneumococcus in the sputum during the two winter seasons. During the two winter seasons 7 out of 9 patients with complete records showed *H. influenzæ* counts which were consistently higher than the pneumococcus counts. In the remaining 2 the pneumococcus counts were high during 1957-58, but were low during the first observation period. The total number of high counts of *H. influenzæ* found in 160 sputum samples

Table I.—Viable Counts of *H. influenzæ* and Pneumococci in 160 Sputum Samples from 9 Chronic Bronchitics

Bacterial composition of sputum	*No. of counts*	*Per cent. of total No. of counts*
No. of H.I.>No. of pneumococci ..	98	61·3
No. of H.I.=No. of pneumococci ..	34	21·3
No. of pneumococci>No. of H.I. ..	26	16·3

H.I.=*H. influenzæ*

from these patients during two winter seasons confirms the pattern seen in individual patients (see Table I).

The counts for 1956-57, both for *H. influenzæ* and for the pneumococcus, were consistently higher than in 1957-58. This made comparisons between the years somewhat difficult, so the *H. influenzæ* counts for 1957-58 were weighted by multiplying by 2·7 and those for the pneumococcus by 1·5.

TABLE II.—AVERAGE OF THE SIX-MONTHLY SPUTUM COUNTS OF *H. influenzæ* AND PNEUMOCOCCI FOR EACH GROUP OF 9 CHRONIC BRONCHITICS DURING TWO WINTER SEASONS

Group of patients	1956-57		1957-58	
	Average No. of H.I./ml.	*Average No. of Pn./ml.*	*Average No. of H.I./ml.*	*Average No. of Pn./ml.*
Treatment ..	835×10^6	168×10^6	613×10^6	101×10^6
Control ..	1138×10^6	167×10^6	1281×10^6	219×10^6

H.I. = *H. influenzæ*; Pn. = pneumococci. The difference between the average counts for the treatment and control groups is not significant statistically.

Comparison of the average number of *H. influenzæ* and pneumococci per ml. of sputum in the treatment and control groups during the two winter periods reveals some reduction of *H. influenzæ* in those under treatment during both periods. The difference in the average number of pneumococci between treated and untreated is variable and might suggest that the incidence of this organism is related to factors other than the use of antibacterial therapy (see Table II).

b. Association of exacerbations with an increase in the number of potential pathogens. The frequency of exacerbations was the same in the treated and untreated groups

TABLE III.—NUMBER OF EXACERBATIONS AND NUMBER OF DAYS OFF WORK, CONFINED TO BED, OR BOTH, IN GROUPS TREATED WITH OXYTETRACYCLINE–TRIPLE SULPHONAMIDE, AND UNTREATED, IN THE PERIODS OCTOBER-MARCH 1956-57 AND 1957-58

	Treatment group	*Control group*
No. of patients	9	9
No. of exacerbations	25	23
No. of exacerbations per patient	2·8	2·6
Total duration of exacerbations (days)	278	211
No. of days off work and/or in bed	115	137
Ratio duration/days off work or in bed	115/278	137/211
	= 0·41	= 0·65

The difference between the ratios : duration of exacerbations/days off work or in bed in the treatment and control groups is significant ($P = < 0{\cdot}001$).

of patients. However, although the total duration of exacerbations was greater in the treatment than in the control groups, the time spent in bed, or off work, or both, was significantly less ($P<0.001$) in the treated patients (see Table III).

At least 4 out of 5 (40 out of 48) of all exacerbations were associated with a high or increased count of *H. influenzæ*, either alone or in conjunction with the pneumococcus. Conversely, 2 out of 5 (21 out of 48) of all exacerbations were associated with a high or increased count of pneumococci, either alone or in conjunction with *H. influenzæ*. No increase of either of these two respiratory, or any of the other three potential pathogens, was observed in six exacerbations all of which occurred in the treatment groups. The difference between the incidence of high or increased counts of *H. influenzæ* in the treated and untreated groups is statistically significant ($P=0.03$), whereas that of the pneumococcus is not significant (see Table IV).

c. Exacerbations and fog. Of a total of 48 exacerbations, 20 (40 per cent.) occurred on or not more than seven days after a foggy day. The incidence of exacerbations was virtually the same in the treated and untreated groups (see Table IV). Furthermore, there was no apparent relation between the incidence of high counts of either *H. influenzæ* or the pneumococcus in exacerbations and the presence or absence of fog.

3. *Increase of Resistance to Oxytetracycline of H. influenzæ Strains during Treatment*

In vitro sensitivity tests of *H. influenzæ* strains to oxytetracycline were carried out by the punch plate method and the final readings were taken from replica plates according to the technique of Elek *et al.* (1953). Pairs of strains were

TABLE IV.—ASSOCIATION OF TWO BACTERIAL PATHOGENS AND FOG WITH EXACERBATIONS OF CHRONIC BRONCHITICS OBSERVED DURING TWO WINTER PERIODS

Type of bacterial counts	*No. of exacerbations in treatment group—*			*No. of exacerbations in control group—*		
	During or after fog	*In absence of fog*	*Totals*	*During or after fog*	*In absence of fog*	*Totals*
High H.I. counts	4	6	10 } 18	5	6	11 } 22
High H.I. and Pn. counts	4	4	8 } 9	4	7	11 } 12
High Pn. counts ..	1	0	1	0	1	1
No bacterial increase ..	2	4	6	0	0	0
Totals	11	14	25	9	14	23

collected from 12 of the patients receiving treatment during one or the other of the winter seasons, and from 8 of the patients in the control group. Of the two strains obtained from each of these 20 patients one was collected and freeze-dried at the beginning and one at the end of the two winter seasons. A five-fold increase of resistance to oxytetracycline was seen in the strains from 2

patients of the treated group, whilst the strains from the 10 remaining treated patients were as sensitive after as before the six months treatment. No increase in resistance was observed in the strains from untreated patients.

Discussion

The results presented show the numerical predominance of *H. influenzæ* over the pneumococcus in the sputa of chronic bronchitics known to harbour this organism. The reduction in the numbers of both these organisms by oxytetracycline in combination with a triple sulphonamide did not prove to be permanent, as their number nearly always increased again when there was an exacerbation. About half as many *H. influenzæ* were counted per ml. of sputum in the treatment group as in the control groups, whilst the changes in the pneumococcus counts were variable Although an exacerbation provokes an increase in the number of *H. influenzæ* and the pneumococcus, treatment leads to a restriction in the increase of the bacterial flora which is statistically significant. Analysis shows that this is due to control of *H. influenzæ* rather than the pneumococcus. These findings do not support the views expressed in the Report of the British Tuberculosis Association (1960) which postulated that small doses of penicillin or oxytetracycline in chronic bronchitics shorten the length of exacerbations by virtue of the suppression of pneumococcus infections while *H. influenzæ* remains uninfluenced; in fact the reverse seems to be true.

The emergence of a few resistant strains is not a very striking one and agrees well with the impressions of Helm *et al.* (1956) and Elmes *et al.* (1957), that resistance of *H. influenzæ* to oxytetracycline does not develop rapidly, and with the observation of Edwards *et al.* (1957) who found either no increase of resistance or at most a fourfold increase in the few cases they examined.

Mulder *et al.* (1952) reported that the use of sufficiently high doses (2 g. daily) of antibacterial agents, including the tetracyclines, could eliminate *H. influenzæ* temporarily from the sputum of most patients. In this investigation, although in some cases the comparatively small dose of oxytetracycline and sulphatriad was sufficient to reduce the number of *H. influenzæ* and the pneumococcus, the concentration of the antibacterial drugs at the site of infection was not adequate to eliminate them. This problem of the maintenance of an adequate concentration of antibacterial drugs in the bronchi or sputum has not received much attention (Zinnemann, 1960), but the administration of larger doses of antibiotics to out-patients with the increased risk of side effects constitutes a major difficulty in investigations of the kind reported here.

In the doses given, oxytetracycline together with a triple sulphonamide had no effect on the frequency of exacerbations, which is contrary to the findings of Buchanan *et al.* (1958). Elmes *et al.* (1957) found loss of time from work a better indicator of antibiotic therapy in chronic respiratory disease and this view is supported by a Report to the Medical Research Council (1959). In our investigation, the ratio of total time spent in bed, off work, or both, to the total duration of exacerbations was significantly less in the treatment groups, which lends support to the findings of Elmes *et al.* (1957), the Reports to the M.R.C. (1957) and to the British Tuberculosis Association (1960).

Although a single causative factor of chronic bronchitis has as yet not been found, bacterial infection, and in particular infection with non-capsulated *H. influenzæ*, plays an important part in the progressive course of this crippling disease. Our results presented in Table IV support this view. As antibiotic therapy can influence only the bacterial flora in the bronchi, our findings suggest that *H. influenzæ* plays a more important part than the pneumococcus in exacerbations of chronic bronchitis. The bacterial flora of the sputum may not necessarily be identical with that of the bronchial tree (Bergman and Colldahl, 1956; Tunevall and Wassermann, 1956; Brumfitt, Willoughby and Bromley, 1957; Lees and McNaught, 1959), but reasonably good agreement between cultures of bronchial aspirations and of sputum samples collected by postural drainage in bronchiectatic children has been shown by Allibone, Allison and Zinnemann (1956). We believe that our sputum cultures provide as reliable a guide to the bacterial pattern in the bronchial tree as is practical to obtain from out-patients.

Although the results presented and conclusions drawn are based upon the complete records of only 9 patients, analysis of the data from the total of 24 patients, including the 15 patients who were irregular attenders, completely mirrors the findings obtained in the smaller series.

The results of significance obtained: the numerical predominance of *H. influenzæ*, reduction by antibacterial treatment of the number of *H. influenzæ* in exacerbations, and of time spent off work or in bed, fell somewhat short of what it had been hoped at the outset to accomplish. The inherent difficulties of investigations in chronic bronchitis are due to the fact that the majority of patients are ambulant and hence the investigators are thus unable to control a number of factors that could decisively influence results. Yet, if we are to gain a real insight into the nature of bacterial infection in chronic bronchitis and into the dynamics of such infection, viable bacterial counts, correlated with régimes of treatment with a variety of antibacterial agents, seem to be an essential. This investigation shows that significant results can be obtained even if there is a considerable wastage of suitable cases owing to irregular attendances, defaulting, hospitalisation, or death.

Summary

1. Viable bacterial counts of *H. influenzæ* and the pneumococcus were carried out on sputa of selected bronchitics producing a purulent sputum and known to harbour non-capsulated *H. influenzæ* most of the time. About half of the patients received continuous treatment with oxytetracycline and a triple sulphonamide during six winter months, the others received indistinguishable dummy capsules and tablets. Therapy was reversed in the following six winter months so that patients who had not been treated previously received treatment and those who had been treated received dummy capsules and tablets.

2. In the majority of bacterial counts *H. influenzæ* was present in considerably greater numbers than the pneumococcus.

3. Long-term, low dosage oxytetracycline–triple sulphonamide therapy does not effect an appreciable reduction of counts of statistical significance during six-months winter periods except when exacerbations occur. This reduction of bacterial counts in exacerbations is confined to *H. influenzæ*.

4. Oxytetracyline–triple sulphonamide therapy, with the comparatively low dosage schedule used, was found to have no effect in altering the incidence of acute exacerbations, but there was evidence to show that it reduced significantly the ratio of total time spent in bed, off work, or both, to total duration of exacerbations.

5. Only 2 out of 12 strains from patients after six months continuous combined oxytetracycline–sulphonamide treatment showed a five-fold increase of resistance to oxytetracycline.

6. The case for quantitative work on the infective factor in chronic bronchitis is discussed and the considerable difficulties of such work on out-patients is shown.

We are indebted to the Nursing Staff at the Leeds Chest Clinic for much co-operation in the procurement of sputum specimens, to Mr. F. Dexter for the freeze-drying of cultures, and to Messrs. Pfizer Ltd. for providing a Pfizer Fellowship for one of us (A.W.C.) to carry out the day-to-day work of the investigation. Our thanks are due to Messrs. Pfizer Ltd., and May and Baker Ltd. for supplying free of charge very generous quantities of Terramycin SF, Sulphatriad, and their identical-looking dummy capsules and tablets.

REFERENCES

Allibone, E. C., Allison, P. R., and Zinnemann, K. (1956): *Brit. med. J.*, **1**, 1457.
Bergman, S., and Colldahl, H. (1956): *Acta allerg. (Kbh.)*, **10**, 63.
Bowers, E. F., and Jeffries, L. R. (1955): *J. clin. Path.*, **8**, 58.
Brumfitt, W., Willoughby, M. L. N., and Bromley, L. L. (1957): *Lancet*, **1**, 1306.
Buchanan, J., Buchanan, W. W., Melrose, A. G., McGuiness, J. B., and Price, A. U. (1958): *Lancet*, **2**, 719.
Edwards, G., Buckley, A. R., Fear, E. C., Williamson, G. M., and Zinnemann, K. (1957): *Brit. med. J.*, **2**, 259.
Elek, S. D., Hilson, G. R. F., and Jewell, P. (1953): *Brit. med. J.*, **2**, 1298.
Elmes, P. C., Fletcher, C. M., and Dutson, A. A. C. (1957): *Brit. med. J.*, **2**, 272.
Helm, W. H., May, J. R., and Livingstone, J. L. (1956): *Lancet*, **1**, 775.
Lees, A. W., and McNaught, W. (1959): *Lancet*, **2**, 1112.
May, J. R. (1954): *Lancet*, **2**, 839.
Mulder, J., Goslings, W. R. O., van der Plas, M. C., and Lopez Cardozo, P. (1952): *Acta med. scand.*, **143**, 32.
Rawlins, G. A. (1953): *Lancet*, **2**, 538.
Report to the Medical Research Council (1957): *Brit. med. J.*, **2**, 255.
Report to the British Tuberculosis Association (1960): *Brit. med. J.*, **1**, 297.
Tunevall, G., and Wassermann, J. (1956): *Svenska Läk. Tidn.*, **53**, 463.
Zinnemann, K. (1960): *Erg. Mikrobiol.*, **33**, 307.

Brit. J. Dis. Chest (1961) **55**, 30.

CHRONIC BRONCHITIS IN AFRICAN MINERS AND NON-MINERS IN NORTHERN RHODESIA

By R. Paul

Director, Pneumoconiosis Medical and Research Bureau, Northern Rhodesia

Chronic bronchitis is a disabling condition which, in several countries, has superseded pulmonary tuberculosis in importance as a disease of the respiratory system. The Ministry of Pensions and National Insurance report that in the year 1955-56 almost 27,000,000 working days were lost as a result of bronchitis in the "insured" population of Great Britain.

At this Bureau 35,000 African mine workers from the six copper mines of Northern Rhodesia are clinically and radiologically examined each year. Over the past fifteen years 100,000 individual African mine workers have been so examined, and it has been our observation that the incidence of chronic bronchitis in this population is very low. All are exposed to silica dust, the maximum permissible limit of which, in the range between 0·4 and 7 microns, is 350 particles per c.c. The free silica content of this fine atmospheric dust as determined by the X-ray diffraction method using the Geiger counter technique varies in the six mines from 19 to 43 per cent. It has been suggested (Pemberton, 1953) that workers exposed to silica dust are more liable to the development of bronchitis, even in the absence of established silicosis. It would be expected, therefore, that chronic bronchitis would be more prevalent in the population of African miners under review.

In order to test the validity of our observation, an investigation was instituted to establish the incidence of chronic bronchitis in African miners and non-miners attending the Bureau in the first few months of 1959. The incidence in 675 deceased African miners was also determined histologically.

Investigation

At their routine clinical and radiological examination, 3,536 African miners and 1,815 non-miners with no dust exposure who attended the Bureau in the early part of 1959 were questioned specifically on:

(*a*) whether or not they had a persistent cough with sputum; and
(*b*) their smoking habits.

There was no selection, and they were therefore a true representative sample of the whole African mining population. If the answer to the first question was in the affirmative, even in the absence of physical signs it was agreed to accept this as being chronic bronchitis if no other reasons for their symptoms were found. Thus, the criterion of diagnosis was in no way stringent. The questions were asked by one observer. All cases of suspected chronic bronchitis were referred to the writer for further questioning and examination. In addition,

(*Received for publication August* 25, 1960.)

any case presenting at routine clinical examination with the physical signs of bronchitis was referred by the examining clinician to the writer for further questioning and investigation.

Results of Investigation

Of the 3,536 African miners who were questioned, only 5 fulfilled the criteria for the diagnosis of chronic bronchitis. One further patient with persistent cough and sputum was known to have bronchiectasis and was not included. Reference to the clinical notes of these five miners showed that for years they had complained of a persistent cough with sputum, and various clinicians had confirmed the diagnosis of chronic bronchitis. All five patients had physical signs indicative of the disease. In addition, 11 miners were referred at routine clinical examination who presented with the physical signs of bronchitis, but these all proved to be acute illnesses of a few days' duration.

In the second group of 1,815 non-miners, no chronic bronchitis as defined was recorded. Three from this group were referred with the physical signs of bronchitis, but they too proved to have acute illnesses of short duration.

The group representative of the mining community had a different age distribution from the non-miners, and were on an average nine years older, having an average age of 38 years as compared with 29·8 years found in the non-miners. As chronic bronchitis tends to occur in the older age groups (Oswald, 1958) the difference in age may account for the fact that no cases of chronic bronchitis were recorded among the non-miners. The effect of the difference can be seen from the fact that when the rates prevailing in the age groups of the miners are applied to the non-miners, only one case of chronic bronchitis would have been expected.

Table I shows the distribution by age and length of dust exposure of the two groups. The number of cases of chronic bronchitis is too small to do more than observe that they occurred in the older group of miners, who consequently had more than a minimal amount of dust exposure: but no case was recorded in

Table I.—Distribution of Chronic Bronchitis in 3,536 African Miners and 1,815 Non-miners

	Dust exposure (*in months*)	*Age* 15-24	*Age* 25-34	*Age* 35-44	*Age* 45-54	*Age* 55-64	*Age* 65+	*Totals*
Miners	0- 59	170	966	224	39	3	—	1,402
	60-119	3	441	385	53	10	2	894
	120-179	—	49	441	226(2)*	19	—	735
	180-239	—	—	154(1)*	209(2)*	36	1	400
	240-299	—	—	8	70	14	2	94
	300-	—	—	—	6	5	—	11
	Total	173	1,456	1,212	603	87	5	3,536
Non-miners	*Dust exposure* Nil	556	892	289	64	13	1	1,815

* Chronic bronchitis

the 105 miners with more than 240 months' dust exposure. If dust is an important ætiological factor, cases would have been expected to have occurred in this group.

TABLE II.—DISTRIBUTION OF CHRONIC BRONCHITIS IN 675 DECEASED AFRICAN MINERS

Dust exposure (in months)	*Age* 15-24	*Age* 25-34	*Age* 35-44	*Age* 45-54	*Age* 55-64	*Age* 65+	*Totals*
0- 59 ..	77(4)*	191(3)*	62(3)*	8	3	—	341
60-119 ..	—	68	83	18(1)*	3	1	173
120-179 ..	—	9(1)*	57(2)*	23	5	1	95
180-239 ..	—	—	23(1)*	20(1)*	5	—	48
240-299 ..	—	—	—	8	5	—	13
300- ..	—	—	—	3	2	—	5
Total	77	268	225	80	23	2	675

* Chronic bronchitis

Table II shows the distribution by age and dust exposure of the 16 cases of chronic bronchitis recorded in 675 deceased African miners. The incidence is higher than that found in the clinical survey in so far as cases showing only the minimal pathological changes of chronic bronchitis have been included. Only two had complained of persistent cough with sputum, and it is presumed that in some the disease was not sufficiently manifest to produce symptoms. In more than half the miners the cause of death was an injury, and they were therefore more representative of a normal population than might be expected. In this group chronic bronchitis was equally distributed between the younger and older age groups, but the majority had only minimal dust exposure. Once again, the numbers are too small to make an accurate assessment of the part played by dust in the development of chronic bronchitis; but the fact that 10 cases out of the 16 had less than 59 months' dust exposure suggests that dust alone was not the important factor. The overall low incidence of the disease was the most important finding of the investigation.

TABLE III

	Vale of Glamorgan Survey			*Leigh Survey*		*Dumfries-shire Survey*	*Present Survey*	
Age	*Bronchitis all groups per* 1,000	*Men with dust per* 1,000	*Men with no dust per* 1,000	*Miners per* 1,000	*Non-miners per* 1,000	*Agricultural community per* 1,000	*Miners per* 1,000	*Non-miners per* 1,000
25	22	0	23	—	—	—	0	0
35	42	0	44	—	—	—	0	0
45	89	125	81	—	—	—	1	0
55	103	241	58	235	107	64	7	0
65	156	167	152	—	—	—	0	0

A comparison of the results recorded in this survey and those recorded by other workers, Higgins *et al.* (1956), Higgins (1957) and Higgins and Cochran (1958), is given in Table III and emphasises the low incidence in the African population surveyed.

Discussion

The striking feature that has emerged from the present investigation is the very low incidence of chronic bronchitis prevailing in a population of African miners and non-miners. We have been unable to produce any evidence to support the contention that the inhalation of silica dust predisposes to the development of the disease. Becklake *et al.* (1959) in South Africa found that in European gold miners with dyspnœa, but without silicosis, the incidence of productive cough with rhonchi was high: they concluded that dust exposure alone was not the cause. Higgins *et al.* (1956) in their survey in Leigh found that there was significantly more chronic bronchitis in miners and ex-miners than in men who had not been exposed to dust, but in the mining group they could show no clear relation between bronchitis and dust exposure. Keatinge *et al.* (1959) in their study of the incidence of bronchitis in foundry men in Derbyshire and Nottinghamshire found little evidence that chronic bronchitis was commoner in foundry men exposed to dust.

In relation to the low incidence found in this survey, smoking habits of the population were surveyed. These are given in Tables IV and V.

From these tables it will be seen that a statistically significantly greater proportion of the non-miners smoked, but the greater proportion of heavy

TABLE IV.—SMOKING HABITS OF 3,536 MINERS AND 1,815 NON-MINERS

	Non-smokers	*Smokers*	*Total*
Non-miners	964 (53·1%)	851 (46·9%)	1,815
Miners	2,134 (60·4%)	1,402 (39·6%)	3,536
Total	3,098 (57·9%)	2,253 (42·1%)	5,351

$X^2 = 25{\cdot}5$. $P < 0{\cdot}00001$. $n = 1$.

TABLE V

	Number of Cigarettes Smoked			*Total*
	1-10	10-20	20+	
Non-miners ..	545 (64%)	237 (27·8%)	69 (8·1%)	851
Miners ..	705 (50·3%)	546 (38·9%)	151 (10·8%)	1,402
Total	1,250 (55·5%)	783 (34·8%)	220 (9·8%)	2,253

$X^2 = 40{\cdot}84$. $P < 0{\cdot}00001$. $n = 2$.

smokers was found to be in the miners. The reason for this is an economic one, the copper miners being the highest paid workers in Northern Rhodesia. Generally their smoking habits are extremely moderate, with a high proportion of non-smokers, and of the total numbers in both groups only 4 per cent. smoked more than twenty cigarettes a day. Abbot *et al.* (1953), Palmer (1954), Leese (1956), Clifton (1956), Brown *et al.* (1957) and Higgins (1959) all found that the incidence of chronic bronchitis was higher in smokers than in non-smokers, and was more prevalent in heavy smokers than light smokers. It is considered that the low incidence of chronic bronchitis found in this survey is due partly to the moderate smoking habits of the population surveyed. Another important factor may be the fact that this population when not at work live in an unpolluted atmosphere and enjoy a climate with long hours of sunshine all the year round and with a complete absence of fog. There are many ætiological factors concerned in chronic bronchitis, of which smoking and atmospheric pollution seem to play an important role.

Sutherland (1960) in his Wyers Memorial Lecture stated that the evidence that dust is a cause or even a part cause of chronic bronchitis is slight. The low incidence observed over the years in African miners exposed to silica dust and the low incidence specifically recorded in this investigation support this view. The importance of dust alone as predisposing to the development of chronic bronchitis has probably been over-emphasised.

Summary

The low incidence of chronic bronchitis found in 3,536 African copper miners and 1,118 non-miners in Northern Rhodesia is recorded. Histological examination of the lungs of 675 deceased African miners also revealed a low incidence. There was little evidence that dust was an important ætiological factor in the development of chronic bronchitis. It is considered that there are many ætiological factors in the development of the disease, of which smoking and atmospheric pollution are probably important.

I am indebted to my colleagues for their helpful criticism and especially to Mr. G. Addison, B.Sc.(Econ.), for his statistical assistance.

REFERENCES

Abbot, S. A., Hopkins, W. A., Van Fleit, W. E., and Robinson, J. S. (1953): *Thorax*, **8**, 116.
Becklake, M. R., Zwi, S., and Sutz, W. (1959): *Brit. J. industr. Med.*, **16**, 290.
Brown, R. G., McKeown, T., and Waitfield, A. G. W. (1957): *Brit. J. soc. Med.*, **11**, 162.
Clifton, M. (1956): *Trans. Ass. industr. med. Offrs.*, **6**, 66.
Higgins, I. T. T. (1959): *Brit. med. J.*, **1**, 325.
Higgins, I. T. T. (1957): *Ibid.*, **2**, 1198.
Higgins, I. T. T., Cochrane, A. L., Oldham, P. D., and Gilson, J. C. (1956): *Ibid.*, **2**, 904.
Higgins, I. T. T., and Cochran, J. B. (1958): *Tubercle*, **5**, 296.
Keatinge, G. F., Burton, E. R., and Hunt, P. J. (1959): *Brit. J. Dis. Chest*, **53**, 333.
Leese, W. L. B. (1956): *Lancet*, **2**, 762.
Ministry of Pensions and National Insurance (1957): Digest of Statistics, Report of the Ministry of Pensions and National Insurance for the Years 1955-56. London.
Oswald, N. C. (1958): In *Recent Trends in Chronic Bronchitis* (p. 12). London: Lloyd-Luke.
Palmer, K. M. V. (1954): *Brit. med. J.*, **1**, 1473.
Pemberton, J. (1953): *Trans. Ass. industr. med. Offrs.*, **3**, 202.
Sutherland, C. L. (1960): *Ibid.*, **10**, 4.

Brit. J. Dis. Chest (1961) **55**, 35.

RHEUMATOID LUNG DISEASE

A CASE REPORT WHICH INCLUDES RESPIRATORY FUNCTION STUDIES AND A LUNG BIOPSY

By Leon Cudkowicz, Irving M. Madoff, and Walter H. Abelmann

From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Medical Services, Boston City Hospital; the Department of Medicine, Harvard Medical School, Boston, Mass.; and the Department of Surgery, Boston University School of Medicine

Rheumatoid involvement of the lung was suspected by Charcot (1881), but its autopsy confirmation depended on the precise and more recent identification of rheumatoid lesions. The characteristic histological features of the cutaneous rheumatoid nodule were established by Collins (1937), and lesions of the same type were subsequently recognised in serous membranes such as visceral pleura (Bennett *et al.*, 1940; Baggenstoss and Rosenberg, 1943; Gruenwald, 1948; Raven *et al.*, 1948; Christie 1954). Ellman, Cudkowicz and Ellwood (1954) described the clinical features of a patient with rheumatoid arthritis and widespread serous membrane involvement, including a persistent left pleural effusion, which at autopsy proved to be related to typical rheumatoid nodules on such structures as the left visceral pleura, pericardium, tricuspid, mitral and aortic valves, as well as on the dura mater.

Apart from the development of rheumatoid nodules on the visceral pleura, areas of fibrinoid necrosis are thought to occur in the collagen structures of the lung parenchyma in some patients with rheumatoid disease, giving rise to the interstitial changes first reported by Ellman and Ball (1948). Caplan (1953) drew attention to the increased incidence of rheumatoid disease in patients with pneumoconiosis.

Aronoff, Bywaters and Fearnley (1955) expressed doubt as to the specificity of these lesions in patients with rheumatoid arthritis and contended that the clinical features, if at all typical, might very well be related to other intercurrent lung lesions, not uncommon in debilitated patients of this type. Their autopsy findings showed, nevertheless, an unusually high incidence of pleural fibrosis. Sinclair and Cruikshank (1956), in an important autopsy study, compared the incidence of lung disease in 90 patients suffering from rheumatoid arthritis with 90 non-rheumatoid patients and noted that pleural lesions were twice as frequent in the former group.

Few reports are available concerning the clinical course of rheumatoid lung involvement, and details in the present patient are of interest, as the lung lesions found at biopsy were reflected in specific lung function tests.

Case History

A 63-year-old widower, a retired foreman in a rubber goods department, who had been well until the age of 50, experienced pain and swelling of the

(*Received for publication August* 8, 1960.)

left ankle for the first time in 1945. This gradually subsided with rest, but a year later arthralgia affected the wrists and both ankles. No swellings were noted and he was able to continue his occupation for five years, in spite of periodic arthralgia. In 1951 admission to the Springfield Hospital, Mass., became necessary because of a sudden painful recurrence of swelling of the left ankle. Again, conservative measures and rest led to subsidence of this swelling and pain, and he remained symptom-free until 1956.

Diabetes mellitus was diagnosed in 1954 and treated with diet alone.

Early in 1956, severe post-prandial epigastric pain necessitated admission to the Massachusetts General Hospital. A cholecystectomy and appendectomy were carried out. Shortly before leaving hospital his wrists became painful and began to swell for the first time. In addition, rheumatoid nodules appeared over the elbows, and the diagnosis of rheumatoid arthritis was made. He was discharged after treatment with heat, splints and salicylates. For about twelve months he was almost symptom-free.

In May 1957 he was admitted to the Quigley Memorial Hospital, Chelsea, Mass., with progressive shortness of breath. A massive right pleural effusion was found, without active joint disease. He developed a cough, purulent sputum and an evening pyrexia. Sputum cultures and cytological examinations for malignant cells were negative. Similarly, bronchoscopy and aspiration of bronchoscopic washings were negative, and guinea-pig inoculation of these washings showed no evidence of tuberculosis. The pleural fluid yielded no organisms on culture or guinea-pig inoculation, and the cytology was unremarkable. After aspiration, the effusion recurred very slowly without producing severe breathlessness. The patient left the hospital in the late summer but needed readmission in September of that year on account of disabling dyspnœa at rest. The clinical examination now revealed bilateral pleural effusions and inactive rheumatoid arthritis. No abnormalities were observed in the cardio-vascular system, and the electrocardiogram was normal. Right thoracentesis yielded a purulent exudate, but no organisms could be seen on smear or culture.

Tests for histoplasmosis and lupus cells were negative. A scalene node biopsy revealed a non-specific inflammatory reaction. The urine examination was normal; Hb 12 g.; Hæmatocrit 41·2%. White cell count was 9,000 with a normal differential count. The ESR (Westergren) was 37 mm. in the first hour. The serum uric acid was 3 mgm. %. Total protein was 6·5 g. % with 3·1 albumin and 3·4 globulin. Serum calcium 9·4 mgm. %, phosphorus 3·9 mgm. %. Blood-urea-nitrogen 10 mgm. %. Serum electrolytes: within normal limits. The patient was given a course of cortisone.

Because of the persistent unusual pleural effusions the patient was transferred to the Boston City Hospital on February 17, 1958.

Special Investigations

Biopsies were taken of the nodules on the left elbow and extensor surface of the left arm, and the microscopy of these indicated rheumatoid nodules.

Roentgenograms of the chest (Figs. 1 and 2) showed extensive pleural thickening and fibrosis involving the lower half of each lung, especially on the right. The heart shadow was normal. Radiographs of the hands and feet showed multiple irregular punched out defects involving the heads of the metatarsal bones, the metatarsal-phalangeal joints and the interphalangeal joints

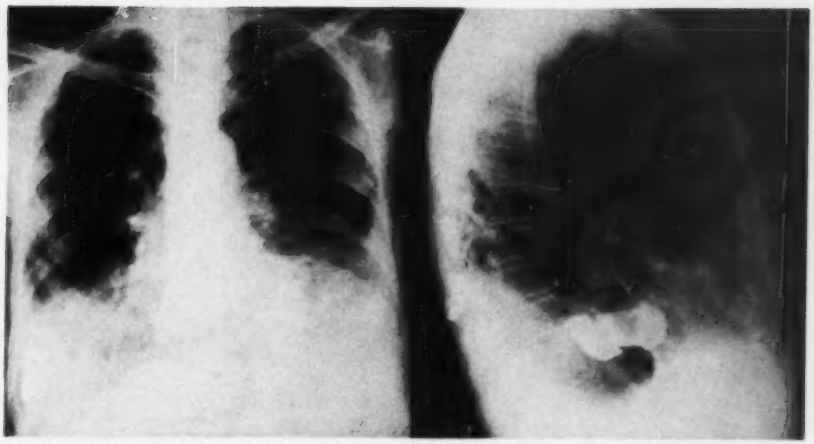


FIG. 1.—Postero-anterior and right lateral chest X-ray films showing bilateral pleural effusions. Residual lipiodol remains in the right pleural space from a previous investigation.

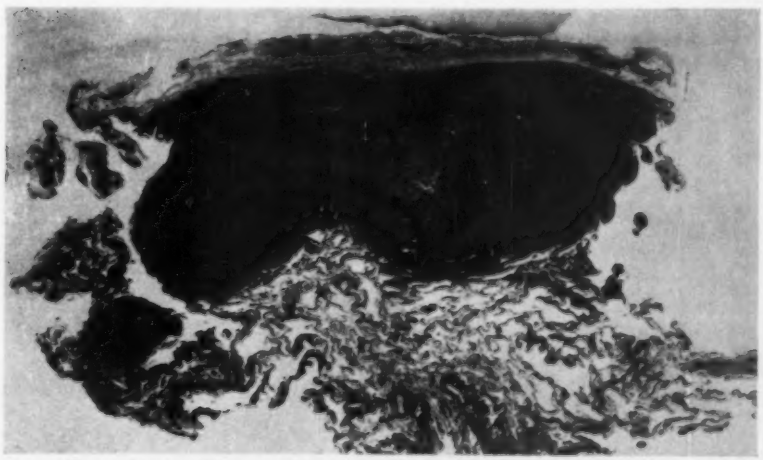


FIG. 2 (×7).—Rheumatoid nodule beneath the right visceral pleura.

To face p. 36

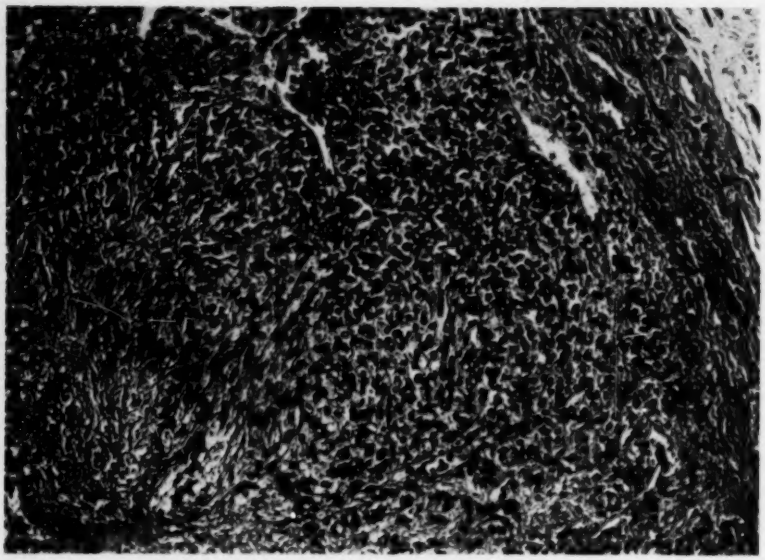


FIG. 3 (×240).—Photomicrograph of pleural rheumatoid nodule, showing, from left to right, (A) area of fibrinoid necrosis, (B) palisading of fibrous tissue, and (C) visceral pleura.

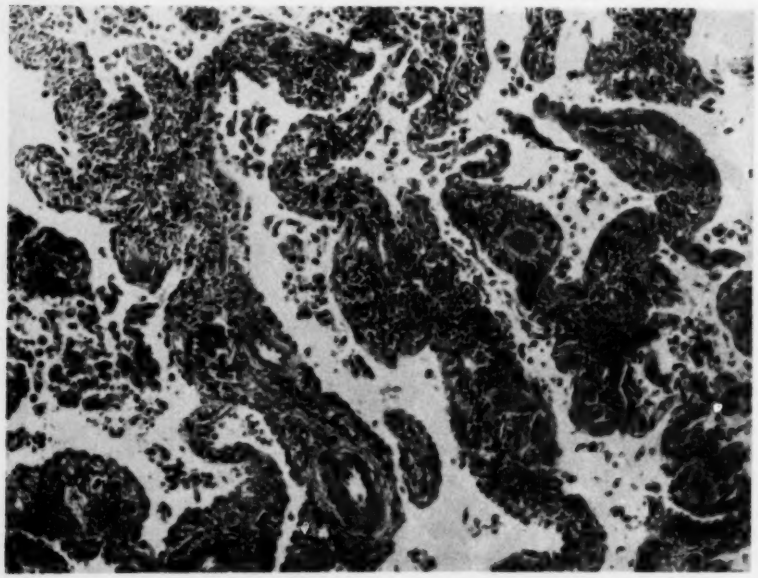


FIG. 4 (×135).—Photomicrograph of lung parenchyma, showing thickened alveolar septa.

of the great toe of each foot. Similar defects were present throughout the fingers of both hands, and there was marked narrowing of the wrist joints.

Bronchoscopy showed no gross abnormalities.

An electrocardiogram showed a semi-vertical heart, T wave inversion in AVF and normal sinus rhythm.

RESPIRATORY FUNCTION TESTS

	Actual values	*Predicted values*
Maximum breathing capacity in litres/minute	52	84
Vital capacity in litres	2·31	3·48
Timed vital capacity as % of total in 1 second	59%	> 75%
Pulmonary mixing index, % alveolar N_2 after 7 minute O_2 breathing	1·3	< 1·5
Tidal volume in ml.	568	
Inspiratory capacity in ml.	1315	
Expiratory reserve volume in ml.	1051	
Residual volume in ml.	2450	1550
Functional residual capacity in ml.	3503	
Total lung capacity in ml.	4816	5029
RV/TLC%	50·8%	30·8%
Carbon dioxide diffusing capacity (single breath) D_{CO} ml./min./mm/Hg	7·7	25 ± 4
Resting ventilatory equivalent for oxygen in lit./100 ml. ..	2·9	2·5

While intrapulmonary mixing appeared to be normal, distension was indicated by the increase in residual volume. Apart from the reduction in expiratory air flow the most significant finding appears to be the marked fall in diffusing capacity.

Cardiac catheterisation showed slight pulmonary hypertension associated with slight increase in pulmonary vascular resistance.

The clinical evidence of rheumatoid arthritis and the absence of heart failure or other gross lung disease suggested that the pleural lesions and effusions might be related to rheumatoid disease. In order to establish this diagnosis a small right-sided thoracotomy was carried out on February 27, 1958. The right chest was entered through the base of the fifth right costal cartilage and rib. Palpation of the middle lobe revealed irregularly firm nodules over the whole of its pleural surface. One of the nodular areas was incised for a distance of 1½ in. and removed.

Biopsy Report

The specimen consisted of a piece of lung and measured 3 × 2·2 × 0·7 cm. The pleural surface was grey and centrally roughened. The lung appeared to be nodular. The sectioned surfaces were airless, grey with punctate black mottling, and showed several firm, pale, subpleural nodules. The largest of these nodules measured 0·7 cm. in its greatest diameter.

All sections from four blocks of lung were similar. The subpleural nodules showed multiple areas of central necrosis, which sometimes became confluent (Fig. 2). Neutrophils were present in the smaller areas of necrosis, while nuclear detritus was scattered through the larger foci. These foci were sur-

rounded by epithelioid cells which frequently assumed a palisade arrangement. A dense infiltrate of lymphocytes and plasma cells surrounded the periphery of the nodules (Fig. 3).

The lung parenchyma adjacent to the nodules also showed considerable changes (Fig. 4). The alveolar septa were thickened and in some cases reached an astonishing breadth. They were infiltrated by plasma cells and occasional clumps of lymphocytes. In places the swollen, densely infiltrated septa and bronchiolar walls protruded in a villous or papilliform fashion into the air spaces. In some of the alveolar spaces aggregates of macrophages were visible. The vascular changes were relatively slight, but there was some thickening of the walls of small arterial vessels.

Final Course

At the end of March 1958 the patient was discharged on a small maintenance dose of Cortisone. In June of that year he developed a left spontaneous pneumothorax followed by an empyema. The empyema was drained but a left broncho-pleural fistula developed. In order to permit this to heal, the steroid therapy was gradually reduced, but the patient rapidly deteriorated and died on August 31, 1958. Autopsy could not be obtained.

Discussion

With the recognition of the essentially systemic distribution of rheumatoid lesions by Ellman and Ball (1948) evidence has gradually accumulated in favour of two distinct types of lung involvement: the formation of necrobiotic nodules on the visceral pleura and adjacent lung, which in the series reported by Christie (1954) varied from 3 mm. to 7 cm. in diameter, and the interstitial parenchymatous lesions first reported by Ellman and Ball. The latter are not necessarily associated with pleural effusions, and their relation to rheumatoid arthritis was questioned by Aronoff *et al.* (1955). The distinct microscopy of the pleural nodules and their close resemblance to rheumatoid nodules elsewhere—as seen in the present case—add support to the existence of pleural involvement in rheumatoid arthritis. Horler and Thompson (1959) found pleural effusions in 9 patients in a series of 180 rheumatoid arthritics. Eight of these patients were men and all of them were over 40 years of age. The patient described by Ellman, Cudkowicz and Ellwood (1954), also a man, developed rheumatoid arthritis at the age of 46, but the left-sided effusion only appeared in the seventeenth year of the disease. The present patient was well until the age of 50, and the pleural effusions occurred twelve years after the first episode of joint swelling. One year before the development of the right effusion rheumatoid nodules were noted for the first time over the elbows. It is not clear from the literature if a relationship exists between the development of joint swellings and parenchymatous lung disease, nor is it clear if pleural effusions follow joint swellings or the development of crops of nodules over the extremities. In the present case as in the patient of Ellman *et al.* (1954) widespread nodules preceded the pleural effusions. Robertson (1952) found 4 out of 58 pleural effusions in patients over the age of 40 to be due to " collagen diseases." This prevalence of effusions in men who develop rheumatoid arthritis after middle

age suggests that nodule formation may be a specific of this disease in this age and sex group, contrasted with the usual manifestations in women in whom the disease predominates.

Respiratory function tests revealed considerable reduction in diffusing capacity. A widespread reduction in diffusion surface as a result of bilateral pulmonary vascular occlusion can probably be ruled out because of the small rise in pulmonary arteriolar resistance. The key to an understanding for this gross reduction in pulmonary diffusing capacity is supplied by the microscopy of the lung parenchyma. This showed widespread thickening and infiltration of the interalveolar septa. The clinical and radiological findings pointed to a bilateral basal localisation of the lesions, which are primarily attributable to the nodular lesions on the pleuræ and adjacent lung, and it becomes necessary to assume that the interstitial parenchymatous lung lesions were much more widespread than could be ascertained from the clinical and radiological examinations of the lungs. In the absence of other ætiological clues, the interstitial lung lesions must be regarded as a feature of the rheumatoid process. If the interstitial parenchymatous lesions develop at a phase of the disease which as yet has not been adequately recognised, repeated diffusion studies in patients with rheumatoid arthritis might be of considerable help, particularly at the time when crops of rheumatoid nodules make their first appearance. Should it emerge that such a defect can already be demonstrated before nodules or pleural effusions occur, then the parenchymatous lesions may be of a different type and belong to a phase of the disease which has so far escaped precise clinical scrutiny.

Summary

The clinical course of a man with rheumatoid arthritis is described. In the twelfth year of the disease he developed bilateral pleural effusions. Pulmonary function tests showed that the pulmonary diffusing capacity was greatly reduced. Lung biopsy demonstrated pleural and sub-pleural necrobiotic nodules of the rheumatoid type and also revealed extensive thickening and infiltration of the interalveolar septa.

The significance of the special investigations in relation to the two distinct types of rheumatoid lung involvement has been discussed.

The authors wish to express their thanks to Drs. E. A. Gaensler and J. V. Macnamara for their assistance with the respiratory function tests, and to Dr. Olga Leary, Jr., for her help in the interpretation of the histopathology.

REFERENCES

ARONOFF, A., BYWATERS, E. G. C., and FEARNLEY, G. R. (1955): *Brit. med. J.*, **2**, 228.
BAGGENSTOSS, A. H., and ROSENBERG, E. F. (1943): *Arch. Path. Chicago*, **35**, 503.
BENNETT, G. A., ZELLER, J. W., and BAUER, W. (1940): *Arch. Path. Chicago*, **30**, 70.
CAPLAN, A. (1953): *Thorax*, **8**, 29.
CHARCOT, J. M. (1881): *Clinical Lectures on Senile and Chronic Diseases*, The New Sydenham Society, London, Vol. XCV, cited by Horler *et al.* (1959).
CHRISTIE, G. S. (1954): *Aust. Ann. Med.*, **3**, 49.
COLLINS, D. H. (1937): *J. Path. Bact.*, **45**, 97.

ELLMAN, P., and BALL, R. E. (1948): *Brit. med. J.*, **2**, 816.
ELLMAN, P., CUDKOWICZ, L., and ELLWOOD, J. S. (1954): *J. clin. Path.*, **7**, 3, 239.
GRUENWALD, P. (1948): *Arch. Path. (Chicago)*, **46**, 59.
HORLER, A. R., and THOMPSON, M. (1959): *Ann. intern. Med.*, **51**, 1179.
RAVEN, R. W., WEBER, F. PARKES, and PRICE, L. W. (1948): *Ann. rheum. Dis.*, **7**, 63.
ROBERTSON, R. F. (1952): *Brit. med. J.*, **1**, 133.
SINCLAIR, R. J. G., and CRUIKSHANK, B. (1956): *Quart. J. Med.*, **25**, 313.

Brit. J. Dis. Chest (1961) 55, 41.

TWO CASES OF PULMONARY TUBERCULOSIS PRESENTING WITH ORAL LESIONS

M. B. Paul and A. C. Bowden
Burton-on-Trent Hospital Group

Tuberculous lesions of the mouth complicating pulmonary tuberculosis are uncommon. Standard textbooks on tuberculosis seldom mention the occurrence of tuberculous lesions above the larynx. Nevertheless they do occur and Cawson (1960) gives the incidence from published surveys as 0·2 per cent. He also states that only two cases have been reported in the United Kingdom since 1949. In view of this it would seem worth reporting the following two cases.

Case 1. A man aged 84 who had been a brewery worker was referred to A.C.B. in December 1958 with an ulcer at the left angle of the mouth of two-three months' duration. The ulcer was 3 cm. in its maximum dimension and involved the mucous membrane and skin. It appeared to be proliferating and was indurated and had the typical appearance of an epithelioma of cheek.

The patient was seen by the radiotherapist, who agreed that the ulcer was an epithelioma. X-ray therapy was begun, but the lesion failed to respond and a biopsy was done and was reported on as follows: " tuberculous ulcer of lip in which acid-fast bacilli in fair numbers were seen."

A radiograph of the chest was then taken and showed bilateral fibrocaseous tuberculosis with cavitation. (Fig. 1.) He was referred to M.B.P. A history of bronchitis most winters was obtained with deterioration in general health during the last twelve months and a more troublesome cough with sputum which was bloodstained on occasions. Sputum was positive for acid-fast bacilli. Examination of the mouth at this stage showed an ulcer at the left angle of the mouth with much slough in the floor and an ulcer on the hard palate. No lesion was visible on the tongue. He was treated with streptomycin sulphate injections 1 g. daily, and Isoniazid tablets, 300 mgm. daily, with rapid and complete healing of his oral lesions. Chest X-ray did not show much change. As the patient developed sensitivity to streptomycin and as he was unable to take oral preparations, chemotherapy was not continued for more than three months. When last seen in July 1960 his mouth remained healed, chest X-ray was unchanged and general condition good considering his age.

Case 2. A man aged 52 who was a farm worker was first seen in January 1960 by A.C.B., to whom he had been referred because of ulceration of the soft palate. He gave a history of " sore throat and difficulty in swallowing " for one month. He had been doing heavy manual work up to two days before, but now " felt tired."

On examination he was edentulous. There was gross ulceration of the soft palate, fauces and throat. The ulcers were deep with a yellow sloughing base,

(*Received for publication October* 7, 1960.)

serpiginous margins, and they were confluent. The cervical glands on the right side were hard and shotty. The condition suggested a blood dyscrasia, but blood count was normal and hæmoglobin 90 per cent. Wassermann and flocculation tests were normal. Blood sedimentation rate was 62 mm. in the first hour. A biopsy of an ulcer was performed. It was not very conclusive histologically, but acid-fast bacilli were found in the sections on special staining.

The patient was then referred to M.B.P. He denied any chest symptoms apart from a cough and a little morning sputum which he had had for a long while. There had been no deterioration in general health and the patient was able to do a full day's work on the farm. X-ray showed bilateral thin-walled cavities in both lungs. These were confirmed by tomograms (Fig. 2). Sputum was positive for acid-fast bacilli on direct smear. On treatment with streptomycin and Isoniazid there was rapid healing of the oral lesions which was complete in six weeks. There was considerable diminution in the size of the pulmonary cavities, but tomograms showed cavities to be still present on 20th April, 1960. Laryngeal swabs were negative for tubercle bacilli. When last seen on 19th September, 1960, the oral lesions remained healed, chest X-ray was unchanged, and the patient was well and fit to resume work.

Discussion

These two cases conform to Cawson's (1960) observations regarding age and sex incidence of tuberculous ulceration in the mouth, though the location of the lesions is uncommon. The response of the oral lesions to specific chemotherapy was as rapid and complete as is expected with ulcerative lesions of mucous membranes. The response of the pulmonary lesions in case 1 was to be expected in view of the long-standing nature of the disease, the age of the patient, and the short course of chemotherapy. In case 2 prolonged chemotherapy is being given and already sputum conversion has been achieved and it is hoped that eventually cavity closure will result.

These two cases confirm the findings of Cawson and re-emphasise the diagnostic problem presented by ulcers of the mouth in general. Despite the rarity of the combination and the fact that extensive pulmonary tuberculosis can exist without any marked chest symptoms the possibility of an underlying tuberculous ætiology should be considered in all cases of extensive ulceration of the mouth.

REFERENCE

Cawson, R. A. (1960): *Brit. J. Dis. Chest*, **54**, 40.

PLATE VI.

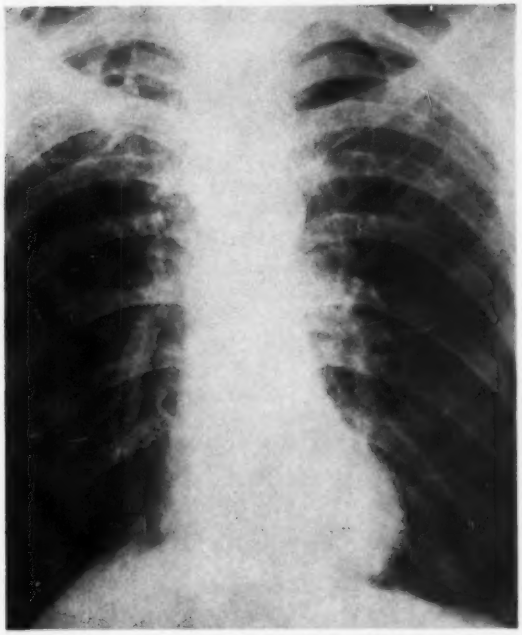


FIG. 1.—P.A. film showing cavitation.

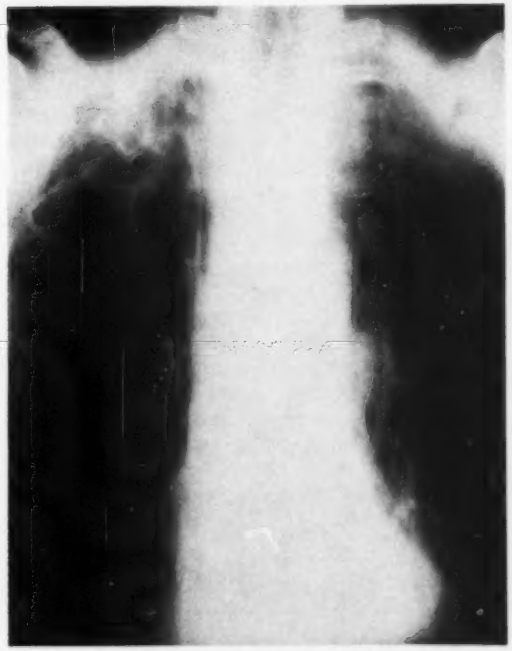


FIG. 2.—Tomogram confirming bilateral thin-walled cavities.

To face p. 42

Brit. J. Dis. Chest (1961) 55, 43.

SOLITARY OIL GRANULOMA OF THE LUNG

A REPORT OF THREE CASES

By Z. Eyal, J. B. Borman and H. Milwidsky

From the Department of Thoracic Surgery,
Rothschild Hadassah University Hospital, Jerusalem, Israel

Despite reports of lung complications following the prolonged administration of mineral oils (Forbes and Bradley, 1958; Hampton *et al.*, 1955; Jampolis *et al.*, 1953; Janes, 1947; Mason, 1955; McDonald and Hodgson, 1954; Siddons, 1958; Annotation *Lancet*, 1951), paraffin is still widely used as a vehicle for nose drops (Sweeney, 1943) or inhalants (Laughlen, 1925), and as a lubricant in the treatment of constipation (Freiman *et al.*, 1940). The aspiration of mineral oil may cause pathological changes in the lung varying from acute lipoid pneumonia to chronic intra-pulmonary granuloma (Graef, 1939; Ikeda, 1937; Pinkerton, 1927; Pinkerton, 1920). Whatever clinico-pathological form these lesions take, they present a problem of diagnosis (Bergh and Burford, 1950; Brown and Biskind, 1941; Buchner and Strug, 1956; Davis *et al.*, 1954; Guidry *et al.*, 1959; Volk *et al.*, 1955). This is especially so in the solitary granulomatous type of lesion, particularly when it occurs in the so-called "cancer age group." We present our experience with three such cases in whom the final diagnosis was only made by thoracotomy.

Case 1. A.H., a 64-year-old male chronic asthmatic, suffered a bout of long-continued fever accompanied by cough and pain in the left chest. This occurred four months before admission to hospital. His condition was diagnosed as pneumonia, but as his symptoms continued despite therapy his chest was X-rayed. A shadow, 5 cm. in diameter with irregular contours, was demonstrated in the left lower lobe (Fig. 1). His E.S.R. was 101 mm. in the first hour (Westergren). Bronchoscopy revealed narrowing of the left lower lobe bronchus above its division into the basal branches. Biopsy from the stenosed area was negative. As primary carcinoma of the lung was suspected, and a left thoracotomy was done. At operation a fibrotic mass was found in the left lower lobe. Macroscopically it did not suggest carcinoma and a wedge resection of the mass was done. Frozen section showed no evidence of malignancy. The post-operative course was uncomplicated.

The histological examination demonstrated a localised area of fibrous tissue proliferation replacing and destroying the alveoli. This tissue was infiltrated by round cells and showed numerous vacuoles of fat lined by mononuclear foam cells and giant cells containing fatty material which proved to be mineral oil. (Figs. 2a and 2b.)

The patient admitted to the long-continued use of paraffin-containing inhalants and nose drops.

Case 2. A.K., a 59-year-old man, was admitted to hospital with cerebral symptoms. Chest X-ray revealed an opacity in the left lower lobe (Fig. 3) and tomography demonstrated linear shadows radiating from the lesion.

(*Received for publication November* 10, 1960.)

Except for vague pains in his left chest he had no symptoms referable to his lungs. The neurological examination was negative, but he was found to be suffering from hypertensive cardio-vascular disease, diabetes and hypothyroidism. E.S.R. was 9 mm. in the first hour (Westergren). Bronchoscopy revealed partial stenosis of the left lower lobe bronchus just below the origin of the segmental bronchus to the apical segment. Biopsy and bronchial washings were negative. As primary carcinoma of the lung could not be excluded, a left thoracotomy was done. A large firm mass with widespread surrounding atelectasis was found in the lower lobe. Lobectomy was performed. The post-operative course was smooth. Microscopical examination revealed the typical findings of an oil granuloma.

For more than twenty years he had used paraffin-containing nose-drops as treatment for chronic sinusitis.

Case 3. M.G., a man aged 57, was X-rayed because of left-sided chest pain. A round shadow was seen in the lingula (Fig. 4). Chest X-ray, a year previously, had been normal. E.S.R. was 25 mm. in the first hour (Westergren). A history of prolonged use of paraffin-containing nose drops was elicited. As the shadow had appeared within the last year and thus lung carcinoma entered into the differential diagnosis, a left thoracotomy was done. Even at operation the diagnosis was uncertain. Frozen section of the mass, removed by wedge resection, revealed no evidence of malignancy. Lingulectomy was completed.

The final histo-pathological examination of the mass demonstrated a paraffin oil granuloma with secondary abscess formation.

Discussion

The three patients described here were between 55 and 65 years—an age group in which solitary lung shadows should be suspected as carcinomatous until proven otherwise. All three had used paraffin-containing nose drops for many years. The first case presented clinically as an unresolved pneumonia, but the dense opacity demonstrated radiologically was suggestive of primary lung cancer. In the second patient the lung lesion was an accidental finding. X-rays done because of chest pain showed a round lung shadow in the third patient. In no patient was physical abnormality of the chest found.

Bronchoscopy revealed partial stenosis of the left lower bronchus in the first and second cases. The negative biopsy and bronchial washings in both cases did not exclude carcinoma. In the third case bronchoscopy was not done as the lesion was situated peripherally. In this case paraffinoma entered into the differential diagnosis, since we knew that the patient had used nose drops for many years. His sputum and bronchial washings were not examined for oil droplets. Even if this examination had been done with a positive result, it would not have changed the indication for thoracotomy, as pulmonary carcinoma could not be excluded. Co-existence of lung cancer and oil granuloma with oil droplets in the sputum has been reported (Sante, 1949; Wagner *et al.*, 1955; Wood, 1943). The possibility of finding oil droplets or oil-containing cells in the bronchial washings and/or the sputum of patients with chronic lipoid granulomas is small (Volk *et al.*, 1955; Wagner *et al.*, 1955).

PLATE VII.

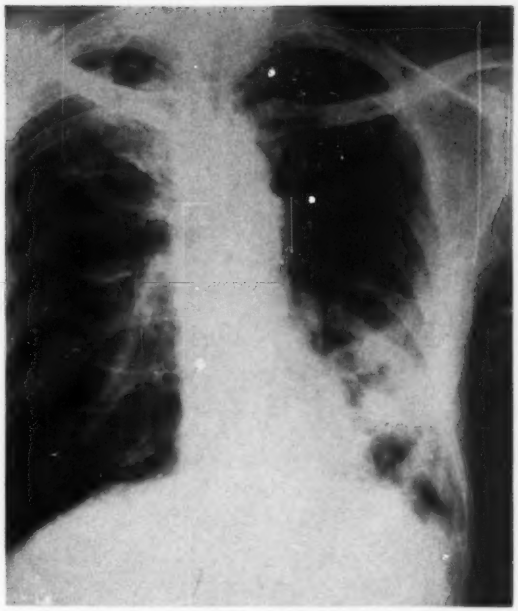


FIG. 1.—Non-homogenous shadow in left lower lobe with irregular contours.

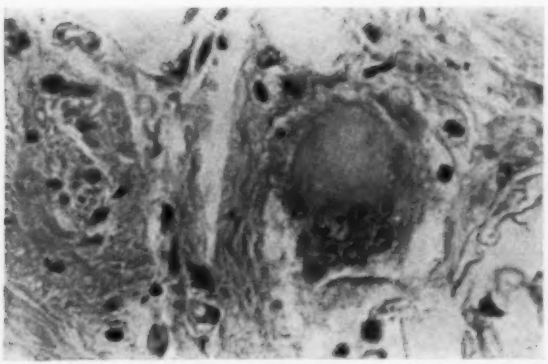


FIG. 2a.—Large fat vacuoles lined here and there by foreign body giant cells and foam cells. Between the fat vacuoles there is proliferation of fibrous tissue infiltrated with round cells (x 100 H.E.).

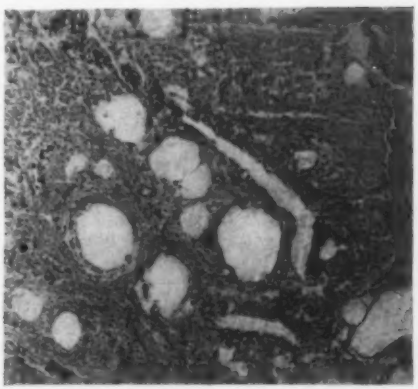


FIG. 2b.—High power magnification shows giant cells containing fat vacuoles. Note proliferation of collagen fibres (x 300 H.E.).

To face p. 44

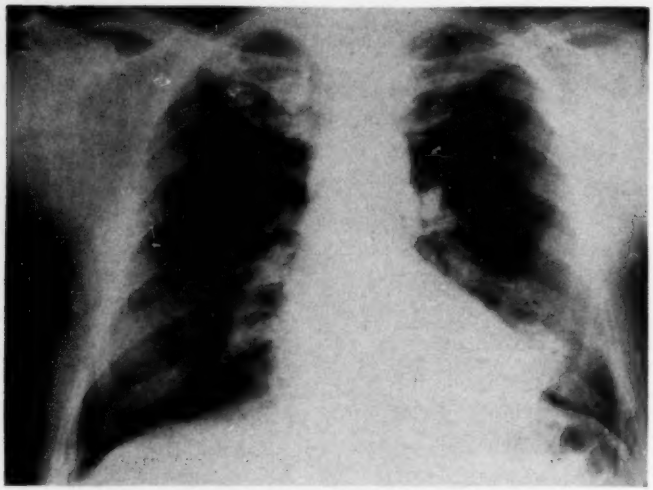


FIG. 3.—Poorly circumscribed opacity in left lower lobe adjacent to heart border. The hilar shadows are calcified lymph nodes.

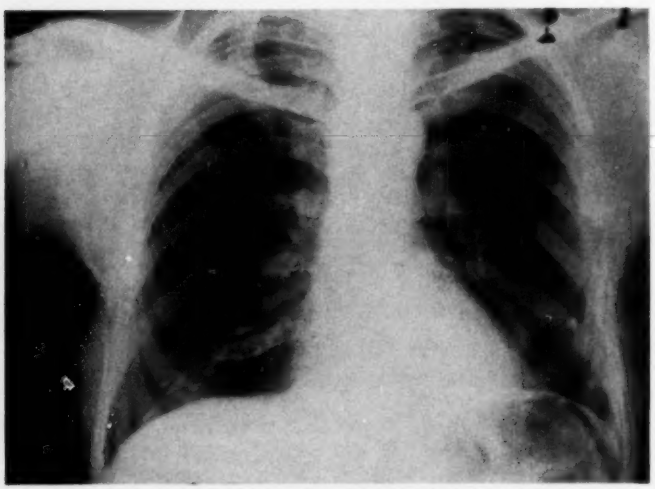


FIG. 4.—Oval peripheral shadow in left lung.

Oil droplets have even been detected in the sputum of patients with normal chest X-rays (Volk *et al.*, 1955).

It is thus obvious that solitary oil granuloma of the lung cannot be diagnosed with certainty by clinical, X-ray or laboratory methods alone. A delay in the diagnosis of an oil granuloma may not be of great importance. However, the erroneous diagnosis of oil granuloma in a patient with bronchogenic carcinoma may be disastrous. Lung cancer is very common in the upper age groups and solitary oil granuloma is rare, and confident diagnosis of an oil granuloma is impossible without thoracotomy. Since the best treatment of lung cancer is early resection, thoracotomy must be done without delay in patients with suspicious solitary lesions. Exploration carries a negligible mortality in expert hands. In addition, it allowed excision of the lesion, thus preventing possible complications (Bordet *et al.*, 1959) due to the broncho-stenosis in the first two cases and the abscess in the third case.

Summary

Three cases of solitary intra-pulmonary oil granuloma occurring in men between 55 and 65 years of age are presented.

The difficulty of differentiation from lung carcinoma is stressed.

Thoracotomy is the only certain way of establishing the correct diagnosis and allowing definitive treatment of the lesion.

We wish to thank Prof. S. Laufer of the Department of Pathology for the histological sections and Mr. Reuveni of the same department for the photographs.

REFERENCES

Bergh, R., and Burford, T. H. (1950): *J. thorac. Surg.*, **20,** 418.
Bordet, F., Daumet, P., Garnier, C., and Paillas, J. (1959): *J. franç. Méd. Chir. thor.*, **13,** 547.
Brown, A. L., and Biskind, G. R. (1941): *J. amer. med. Ass.*, **117,** 4.
Buchner, H. A., and Strug, L. H. (1956): *Dis. Chest*, **29,** 402.
Davis, E. W., Hampton, A. D., Bickham, C. E., and Winship, T. (1954): *J. thorac. Surg.*, **28,** 212.
Forbes, G., and Bradley, A. (1958): *Brit. med. J.*, **II,** 1566.
Freiman, D. G., Engelberg, H., and Merrit, W. H. (1940): *Arch. intern. Med.*, **66,** 11.
Guidry, L. D., Clagett, O. T., McDonald, J. R., and Kincaid, O. W. (1959): *Ann. Surg.*, **150,** 67.
Graef, J. (1939): *Arch. Path.*, **28,** 613.
Hampton, A. D., Bickham, C. E., and Winship, T. (1955): *Amer. J. Roentgenol.*, **73,** 938.
Ikeda, K. (1937): *Arch. Path.*, **23,** 470.
Jampolis, R. W., McDonald, J. R., and Clagett, O. T. (1953): *Intern. Abstr. Surg.*, **97,** 105.
Janes, R. M. (1947): *J. thorac. Surg.*, **16,** 451.
Laughlen, G. F. (1925): *Amer. J. Path.*, **1,** 407.
Mason, J. M. (1955): *Ann. Surg.*, **141,** 940.
McDonald, J. R., and Hodgson, C. H. (1954): *Med. Clin. N. Amer.*, **38,** 989.
Pinkerton, H. (1920): *Arch. Path.*, **5,** 380.
(1927): *Amer. J. Dis. Child*, **33,** 259.
Sante, L. R. (1949): *Amer. J. Roentgenol.*, **62,** 788.
Siddons, A. H. M. (1958): *Brit. med. J.*, **I,** 305.
Sweeney, W. J. (1943): *Eye, Ear, Nose Thr. Monthly*, **22,** 335.
Volk, B. W., Losner, S., Lewitan, A., and Nathanson, L. (1955): *Amer. J. Surg.*, **89,** 158.
Wagner, J. C., Adler, D. J., and Fuller, D. N. (1955): *Thorax*, **10,** 157.
Wood, E. H. (1943): *Radiology*, **40,** 193.
Intrinsic and Extrinsic Lipoid Pneumonia. Annotation (1951): *Lancet*, **261,** 70.

Brit. J. Dis. Chest (1961) **54**, 46.

REVIEWS OF BOOKS

Surgical Anatomy of the Bronchovascular Segments. WILLIAM E. BLOOMER, AVERILL A. LIEBOW and MILTON R. HALES. Illinois: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 267, 208 figs. £6 12s.

It is some years since a book appeared describing bronchial anatomy. The work under review combines a very detailed description of the bronchial tree with a similarly detailed description of the pulmonary arteries and veins. This has probably never been attempted before and is something which is long overdue.

The terminology used is that of Jackson-Huber and Boyden. This departs very little from that which was agreed by the Thoracic Society of Great Britain and the International Congress of Oto-Rhino-Laryngologists. (The adjective "superior" is preferred to "apical" for the apical segment of the lower lobe.)

The work is based on detailed examination of a large number of lungs, and an ingenious "formula" system is used for the description of the bronchi: this saves a large amount of repetition and probably makes the book more readable.

Each lobe is described separately and the common variations from the normal pattern are given. The segmental vessels are also described, and the surgical problems presented by each individual bronchopulmonary segment are discussed.

At the end of the book there are sections concerned with bronchographic and angiocardiographic appearances, and here the high standard of illustration maintained in the rest of the book is not achieved. A number of references relating to the anatomy, the development and the surgery of individual lobes and segments is given at the end of the book.

There are profuse and beautiful illustrations both photographic and diagrammatic, and no less than 168 stereographic transparencies are obtainable separately which exactly match the illustrations in the text.

This book has been designed as a guide to the dissection of the bronchovascular segments, and admirably achieves this purpose.

J. S. BELCHER.

New Virus Diseases. Clinical Differentiation of Acute Respiratory Infections. JOHN M. ADAMS. New York: The MacMillan Co. 1960. Pp. 292. $75.

Before the advent of specific chemotherapy for respiratory tract infections, causal bacteria were identified so that appropriate antisera could be administered. This form of treatment was proving successful in the management of pneumococcal pneumonia when the sulphonamides were introduced and superseded it. In the succeeding quarter of a century, antibiotics helped to minimise the seriousness of bacterial infections of the lung, and instead, attention was focused on the virus disorders of the respiratory tract.

Most viruses are insensitive to antibiotics, so that in this field we are now at a stage somewhat similar to the presulphonamide era, except that the causal organisms are smaller. Once again it has become necessary to define the causes

of numerous acute respiratory disorders, for an ætiological classification forms the only rational basis for an understanding of these diseases, and for the application of anti-viral therapy in the years to come.

The monograph under review surveys the field authoritatively, lucidly, and effectively, in nine chapters. Bacterial and fungal infections of the respiratory tract are dealt with in a chapter apiece. The clinical features, the epidemiology, the laboratory diagnosis, and the prevention and treatment of the various infections are described, and an adequate list of references (with titles) is given at the end of each chapter.

It is hoped that this book will persuade chest physicians to make more determined efforts to seek laboratory confirmation of suspected virus infections of the respiratory tract. An increase in the demand for these services can but lead to their expansion and to increased efficiency, with a better understanding of these undifferentiated clinical syndromes.

D. GERAINT JAMES.

L'Hippocratisme Digital. L'Osteo-arthropathie hypertrophiante et les autres dysacromélies apparentées. By CHARLES COURY. Paris: Masson et Cie. 1960. Pp. 230.

Readers of this journal will have read Dr. Coury's article on "Hippocratic fingers and hypertrophic osteoarthropathy" in the July 1960 issue. That article was, in effect, a summary or, more correctly perhaps, a condensation of his book, "L'Hippocratisme Digital," in which he gives a full account of his material and surveys the literature on clubbing and related phenomena. These he proposes to group together as the "dysacromelias," a term he has coined to emphasise their common basis. There is a good historical introduction, a review of what is known of the pathogenesis, and excellent chapters on the clinical manifestations, in particular the "rheumatic" ones. The bibliography has been gleaned from a wide and representative field, though there are several omissions, *e.g.* those on plethysmographic studies. Particularly curious is the illustration of "Lovibond's sign," without a reference to the original article on which this is based!

In spite of the fact that we learn no more than we know about the causation of the "dysacromelias" this book is certainly a very good review of a fascinating subject which is of such great interest to all who work in the field of thoracic disease, and indeed to rheumatologists and general physicians as well.

L. J. GRANT.

Traitement de l'insuffisance respiratoire. Rapports presentes au XXXIIe Congrès français de médecine—Lausanne, 1959. Paris: Masson et Cie. 1960.

This volume contains the full text of the papers presented at the symposium on respiratory insufficiency held by the Association of French-speaking physicians at their congress in Lausanne in 1959. The subjects include: 1. Pathological physiology (P. Sadoul *et al.*), a very full analysis of over 100 pages; 2. Clinical aspects (P. Bandraz); 3. Treatment of the acute state (P. Mollaret *et al.*), based on the practice of the Claude Bernard Hospital,

Paris; 4. Asthma (Pasteur Valery-Radot *et al.*); 5. Surgical aspects (J-C Rudler *et al.*); 6. Hypersensitivity states (R. Pautrizel *et al.*).

Like all proceedings of this kind, the material is very uneven in presentation, ranging from the most elementary, to the most abstruse with much verbosity and repetition. Nevertheless there is a great deal of interest here.

L. J. GRANT.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

Proceedings of the Pneumoconiosis Conference, held at the University of Witwatersrand, Johannesburg, 1959. Edited by A. J. Orenstein. London: J. and A. Churchill Ltd. Illus. 120s.

Atlas of Exfoliative Cytology, Supplement 2. By George N. Papanicolaou. Harvard University Press; London: Oxford University Press. 44s.

Pages in the History of Chest Surgery. By Nissen and Wilson. Oxford: Blackwell Scientific Publications Ltd. 60s.

To face last page of text

London: Printed in Great Britain for Baillière, Tindall & Cox Ltd., 7 and 8 Henrietta Street, Covent Garden, W.C.2, by Billing & Sons Ltd., Guildford and London. Entered as Second Class Matter at the New York, U.S.A., Post Office.

London: Printed in Great Britain for Baillière, Tindall & Cox Ltd., 7 and 8 Henrietta Street, Covent Garden, W.C.2, by Billing & Sons Ltd., Guildford and London. Entered as Second Class Matter at the New York, U.S.A., Post Office.